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(54) Pyridine derivatives, pharmaceutical compositions comprising the same, the use of the same for the manufacture of medicaments having therapeutic or preventative value, and a process for preparing the same

Pyridin-Derivate, deren pharmazeutische Zusammenstellungen, deren Anwendung für die Herstellung von Arzneimitteln mit therapeutischem oder vorbeugendem Wert und Verfahren zu deren Herstellung

Dérivés de pyridine, leurs compositions pharmaceutiques, leur utilisation pour la fabrication de médicaments ayant une valeur thérapeutique ou préventive, et un procédé pour leur préparation

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Remarks:

- Divisional application 91117132.0 filed on 13/11/87.
- The file contains technical information submitted after the application was filed and not included in this specification

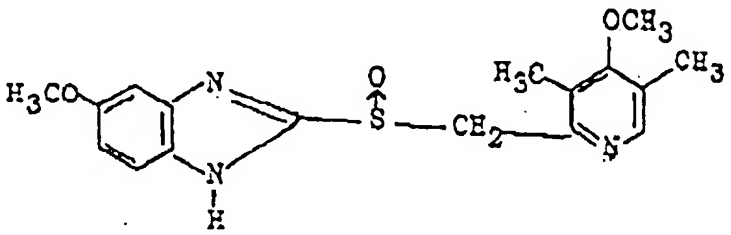
Description

Novel pyridine derivatives exhibiting activity in treating or preventing peptic ulcers, pharmaceutical compositions containing them, and methods of medical treatment are described,

Duodenal and gastric ulcers, known collectively as peptic ulcers, are localized erosions of the mucous membrane of the duodenum or stomach, respectively, which expose the underlying layers of the gut wall to the acid secretions of the stomach and to the proteolytic enzyme pepsin. They are believed to be caused by autolysis which is caused by an imbalance between offensive factors, such as acid or pepsin, and defensive factors, such as resistance of the mucous membrane, mucilage secretion, bloodstream or control of the duodenum. Peptic ulceration is the most common disease of the gastro-intestinal tract and it is estimated that approximately 10 to 20% of the adult male population will experience at some time in their lives.

Peptic ulcers are cured or prevented by medical treatment, in principle, and many pharmacotherapies have been suggested, some with high degrees of success.

Clinically useful modialities include H_2-blockers, such as cimetidine and ranitidine, as anti-ulcer agents. It has been noted, more recently, that inhibitors of H^+-K^+-ATPase, an enzyme specifically present in the parietal cells of the stomach, can effectively inhibit the secretion of gastric acid in mammals, including man, therefore it has been expected that a new class of anti-ulcer agents from this viewpoint will come into existence. More specifically, a wide variety of compounds having a benzimidazole structure have been proposed. Among these compounds is Omeprazole, currently under active development, as the most promising compound; see U.S. Patent Nos. 4,337,257; 4,255,431; and 4,508,905. These patents describe compounds with a methoxy group in the 4-position of the pyridine ring, Omeprazole, having the formula:



and further 2-(4-methoxyethoxypyridine-2-yl)-methylsulfinyl-5-methyl-1H-benzimidazolein the working examples thereof.

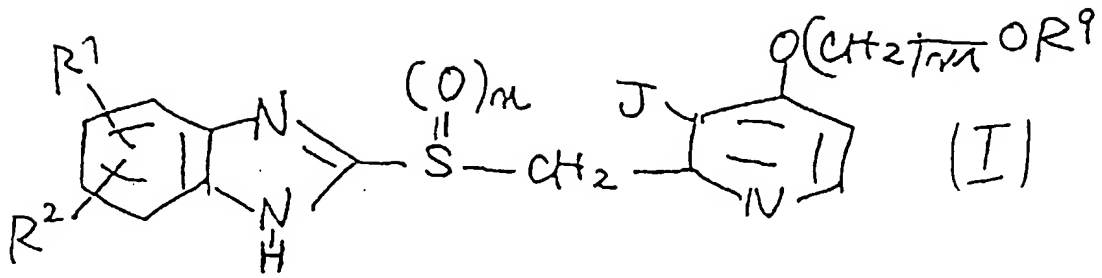
Related benzimidazole-type compounds having anti-ulcer activities are described in published application GB 2,134,523A. More specifically, compounds in which the 4-position of the pyridine ring is substituted with an alkoxyalkoxy group with each alkoxy group containing 1-2 carbons are described. Example 157 of this patent describes 2-(3,5-dimethyl-4-methoxyethoxypyridine-2-yl)methylsulfinyl-5-phenyl-1 H-benzimidazole. Other substitutions on various positions of the benzyl and pyridine rings are also described.

Biological tests reported in tables 4 and 5 of this published application report significant biological effects on gastric acid secretion, both in isolated cells and in laboratory animals, when the 4-position on the pyridine ring is substituted with a methoxy group.

Additional benzimidazole-type compounds, in which the substituent at the 4-position on the pyridine ring is a benzyloxy group, are described in European patent application 0,167,943.

The present inventors have discovered a class of novel compounds with a more excellent anti-ulcer activity than Omeprazole which is regarded, at the present time, as the most significant benzimidazole-type compound having anti-ulcer activity. As a result of intensive studies, it has been found that compounds represented by formula (I) are more potent in inhibiting gastric acid secretion in comparison with Omeprazole. The present invention has been accomplished on the basis of this finding.

The present invention includes a class of pyridine derivatives represented by the general formula:



(I)

wherein R^1 and R^2 may be the same or different from each other and each stand for a hydrogen atom, a C_1-C_6 alkyl, C_1-C_6 alkoxy, halogenated C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl or carboxyl group or a halogen atom

J is a C_1-C_6 alkyl,
R^9 stands for a hydrogen atom or a C_1-C_6 alkyl group,
n stands for an integer of 0 to 2,
m stands for an integer of 2 to 10,

with the proviso that when R^9 is a C_1-C_6 alkyl group, m stands for an integer of 3 to 10, and a pharmaceutically acceptable salt thereof.

The same definitions for R^1, R^2, n, J, R^9 and m are used throughout the specification that follows and in the appended claims.

Also disclosed are pharmaceutical compositions containing these compounds as the active ingredient(s) and the use of a pyridine derivative according to the present invention for the manufacture of a medicament for the treatment or prevention of peptic ulcers in mammals, including humans.

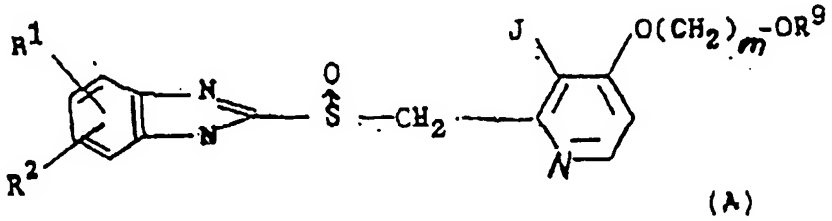
In the definition of the compounds of general formula (I) given above, the lower alkyl group defined above with respect to R^1, R^2 and J in the compound (I) of the present invention is a straight-chain or branched alkyl group having 1 to 6 carbon atoms. Examples include methyl, ethyl, n-propyl, n-butyl, isopropyl, isobutyl, 1-methylpropyl, tert-butyl, n-pentyl, 1-ethylpropyl, isoamyl and n-hexyl groups, among which methyl and ethyl groups are most preferred.

The lower alkoxy group and the lower alkoxy moiety of the lower alkoxycarbonyl group defined above with respect to R^1 and R^2 may be an alkoxy group derived form the above lower alkyl group. Methoxy and ethoxy groups are most preferred.

The halogen atom defined above includes chlorine, bromine, iodine or fluorine.

As for R^1 and R^2, hydrogens for both and then a combination of a C_1-C_6 alkyl, inter alia methyl, for R^1 and hydrogen for R^2 are preferred. A preferred value for n is 1. J is a C_1-C_6 alkyl group, inter alia methyl. Most preferably J is methyl.

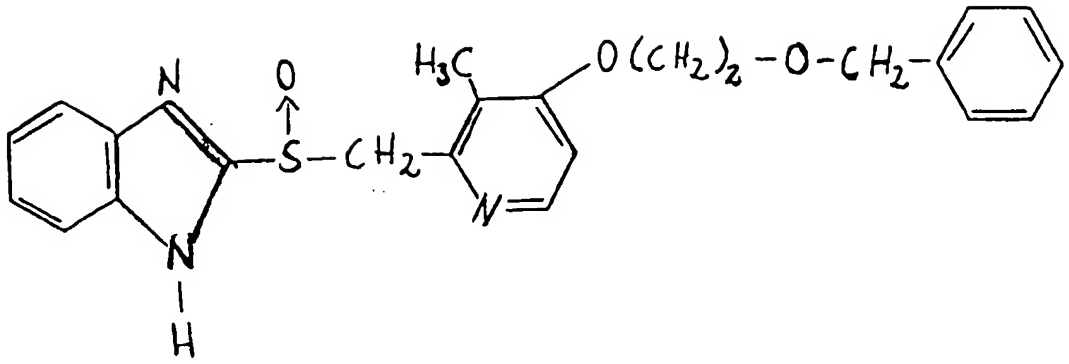
A first preferred class of compounds falling within the compounds of general formula (I) are represented by the following formula:



(A)

(wherein R^1, R^2, J, m and R^9 have the same meanings as defined above). In formula A, the preferred R^1 and R^2 substituents are both hydrogen, or R^1 is 5-C_1-C_6 alkoxy, 5-C_1-C_6 alkyl or 5-halogenated C_1-C_6 alkyl and R^2 is hydrogen. The preferred substituent for J is methyl; the preferred value for m is in the range of 3 to 10, the most preferred being 3; and the R^9 substituent is C_1-C_6 alkyl, inter alia methyl. Among these possibilities for the compounds of formula A the preferred combination is when R^1 and R^2 are both hydrogen, J is methyl, m is 3 and R^9 is methyl.

A preferred compound is a pyridine derivative of the structural formula



Examples of pharmaceutically acceptable salts include salts with inorganic acids, such as hydrochloride, hydrobromide, sulfate and phosphate; those with organic acids, such as acetate, malcate, tartrate, methanesulfonate, benzenesulfonate, and toluenesulfonate; and those with amino acids such as arginine, aspartic acid and glutamic acid.

The compounds according to the present invention can form a salt with a metal such as Na, K, Ca or Mg. Those metal salts are also included among the pharmaceutically acceptable salts of the present invention.

Although the compounds of the present invention may also be present as a hydrate or as a stereoisomer, it is a matter of course that these hydrates and stereoisomers are also included in the scope of the present invention.

Now, the effect of the compounds of the present invention will be described by referring to the following pharmacological experiments.

Pharmacological Experiment

Inhibition against the activity or H^+-K^+ ATPase

(1) Preparation of H^+-K^+ ATPase

Prepared from the fundic glands of a fresh mucous membrane of a pig stomach according to a modified method of Saccomani et al. (see Biochem. and Biophys. Acta, 464, 313 (1977)).

(2) Measurement of the activity of H^+-K^+ ATPase

The compound of the present invention was incubated at various concentration in a 40 mM Tris-HCl buffer solution having a pH of 7.40 together with H^+-K^+ ATPase and 10 µg/ml of a protein at 37°C for 30 minutes, followed by the addition of 15 mM KCl. After 10 minutes, the ATPase reaction was initiated by the addition of 3 mM of $MgCl_2$ and ATP. After 10 minutes, the amount of the released inorganic phosphoric acid was determined according to the method of Yoda and Hokin (see Biochem. Biophys. Res. Com., 40, 880 (1970)).

The test compound was used as a solution in methanol.

The inhibitory effect was determined by subtracting the amount of the released inorganic acid observed with respect to the case wherein a solution of a test compound was added from that with respect to the control wherein only a solvent was added to determine a difference and dividing this difference by the latter amount and shown by percentage. The inhibitory effect is shown in Table 1 in terms of IC_{50}.

(3) The results are shown in Table 1.

Table 1

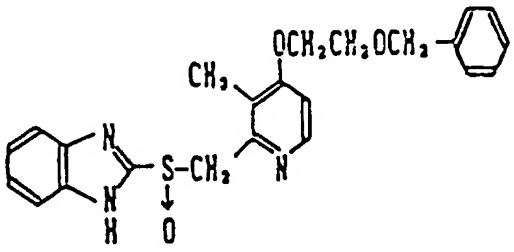
No.	Compound	IC_{50} (M)
1		9.2×10^{-7}

Table 1 (cont'd)

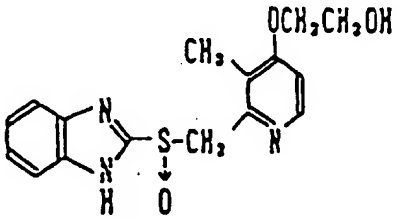
2		1.9×10^{-6}

Table 1 (cont'd)

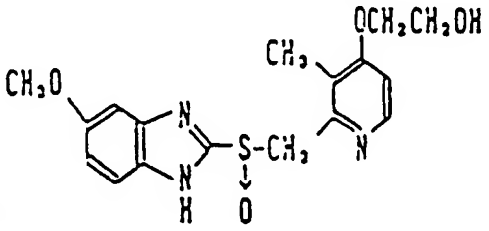
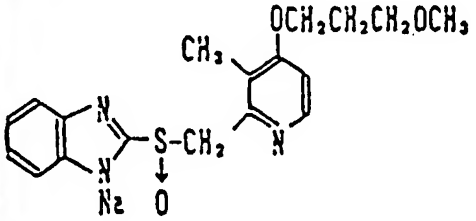
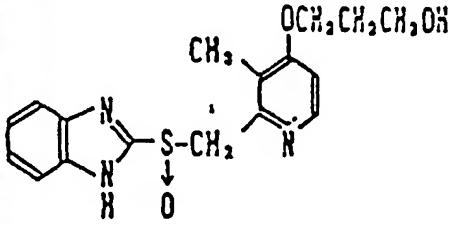
No.	Compound	IC_{50} (M)
3		3.5×10^{-6}
4		1.7×10^{-6}

Table 1 (cont'd)

No.	Compound	IC_{50} (M)
5		1.9×10^{-6}
	Omeprazole	1.1×10^{-5}

It is apparent from the results of the experiments that the compound of the present invention exhibits a high inhibitory effect on the activity of H^+-K^+ ATPase and is highly safe, so that it can effectively inhibit the secretion of an acid and is therefore effective in the therapy or prevention of human and animal peptic ulcer.

Further, the compound of the present invention exhibits excellent recovery of the secretion of an acid and therefore is superior to the one of the prior art in this respect.

Chronic gastric fistula dogs were used. The test compound was intraduodenally administered to each dog in an amount of 4 mg per kg. In 1, 24, 48 and 72 hours, respectively, from the time of administration, pentagastrin (6 micron grams per kg) was injected intramuscularly into the dog. Gastric acid secretion, determined and recovery thereof, was

determined in terms of percent of the control response. Results from this test are shown in Table 3.

From the results, it can be determined that within one hour from the intraduodenal administration the pentagastrin-stimulated gastric acid secretion was completely inhibited in both tests of compound 4 and Omeprazole. In the test, acid output with compound 4 was 61.9 percent and 121.5 percent in comparison with the control group after 24 and 48 hours, respectively. On the other hand, in the same test using Omeprazole, gastric acid secretion was 108.4 percent after 72 hours. With both compound 4 and Omeprazole, 48 hour: and 72 hours were required for the acid secretion to recover, respectively.

Pharmacological Experiment 2 -

Inhibitory effect on gastric acid secretion

Chronic gastric fistula dogs were used. Gastric acid secretion of each dog was stimulated by infusing 100 micron grams per kg per hour of histamine. After one hour of histamine infusion, each of the test compounds was administered intraduodenally to each dog, and after one hour of administration, the amount of gastric acid secretion of each test dog was determined. Results ware compared with the control group to which no test compound had been administered and are expressed in terms of percent inhibition.

The inhibitory effect exhibited by the test compound of the histamine-stimulated gastric acid secretion of the chronic gastric fistula dogs is shown in Table 2. The values of ID 50, calculated from the dose-inhibition curve of the test compounds, are 59.9 micron grams per kg for compound 4 and 112.2 micron grams per kg for Omeprazole, demonstrating that compound 4 was two times more potent than Omeprazole. Compound 4 is shown in Table 1 of Experiment 1 and in working example 33 shown below.

Table 2

μg/Kg	% Inhibition of acid output	
	compound 4	omeprazole
31.25	34.4	-
62.5	50.1	41.1
125	67.7	48.6
250	87.4	62.1
500	100.0	91.2
1000	-	100.0

Table 3

Compound	1 hr	24 hr	48 hr	72 hr
compound 4	0	61.9	-	-
Omeprazole	0.3	32.3	69.1	108.4

The results of the three pharmacological experiments as reported above demonstrate that the compound of the

invention exhibits a significant inhibitory effect on the activity of H^+-K^+ATPase.

Among these compounds, compound 4 of the invention unexpectedly has a more potent inhibitory activity on gastric acid secretion as compared with Omeprazole, which itself is highly inhibitory of gastric acid secretion among the compounds having a benzimidazole-type structure.

Further, it should be noted that the compound of the present invention unexpectedly exhibits a faster recovery or resumption of gastric acid secretion than Omeprazole.

At present, this H+-K+ATPase-inhibiting agent is believed to have a more potent inhibitory activity against gastric acid secretion than an H_2-blocker compound, and thus, in the future, may be the drug of choice for the treatment of ulcers.

But, while more potent inhibitory activity against gastric acid secretion is desirable, too long-lasting inhibition of gastric acid secretion is not preferable for in anti-ulcer agent. For example, it gives rise to the proliferation of Enterochromaffin-like cells (ECL cell) and formation of carcinoid derived from hypergastrinemia; see "Digestion", vol. 35, suppl. 1, page 42 to 55 (1986); the increase in the gastric bacterial flora and endogenous production of N-nitro compounds; see "Brit. Med. J.", vol. 289, page 717 (1984); and difficulty in determining the appropriate dosage regimen.

Thus, an H^+-K^+ATPase-inhibitory agent which possesses an excellent recovery of gastric acid secretion is most preferred.

No toxicological influence has been observed for compound 4 (working example 33), which is a representative compound of this invention, in beagle dogs to which it was orally administered at 10 mg/kg per day for one week, and in rats to which it was orally administered at 50 mg/kg per day for one week.

Thus, compound 4, as representative of this invention, exhibits a significant inhibitory effect upon the activity of H^+-K^+ATPase coupled with the desirable property of excellent gastric acid secretion recovery.

Compound 4, as representative of the compounds of this invention, is thus considered to be effective in the treatment or prevention of peptic ulcers (stomach ulcers and duodenal ulcers) in animals, including humans.

The compounds of the present invention are administered for the therapy or prevention of peptic ulcers either orally as powders, granules, capsules or syrup, or parenterally as an injection, or as an external preparation or drop, or as a suppository. Although the dose remarkably varies depending upon symptoms, age or kind of ulcer(s), it may be about 0.01 to 200 mg/kg, preferably 0.05 to 50 mg/kg, still preferably 0.1 to 10 mg/kg a day, and may be administered in a single dose or in divided doses, for example from 2 to 4 times a day.

The drug may be formulated into pharamceutical presentations using conventional formulation procedures. More specifically, a solid drug for oral application can be prepared by mixing an active principle with filler and, if necessary, binder, disintegrating agent, lubricant, coloring agent, corrigent or the like and converting the obtained mixture into a tablet, coated tablet, granule, powder or capsule.

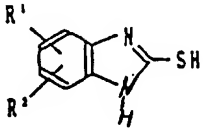
Examples of the filler include lactose, corn starch, sucrose, glucose, sorbitol, crystalline cellulose and silicon dioxide, while those of the binder include polyvinyl alcohol, polyvinyl ether, ethylcellulose, methylcellulose, acacia, tragacanth, gelatin, shellac, hydroxypropylcellulose, hydroxypropylstarch and polyvinylpyrrolidone. Examples of the disintegrating agent include starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium hydrogencarbonate, calcium citrate, dextrin and pectin, while those of the lubricant include magnesium stearate, talc, polyethylene glycol, silica and hardened vegatable oils. The coloring agent may be any one which is permitted to be added to drugs. Examples of the corrigent include cacao powder, mentha herb, aromatic powder, mentha oil, borneol and powdered cinnamon bark. Of course, these tablets and granules may be, if necessary, coated with sugar, gelatin or the like.

The injection can be prepared by mixing an active principle with pH adjusting agent, buffer, stabilizer, solubilizing agent or the like and treating the obtained mixture according to an ordinary process to obtain a subcutaneous, intramuscular or intravenous injection.

Preparation process

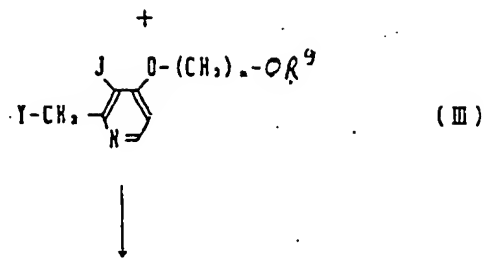
The compound of the present invention can be prepared by various processes, representative examples of which will now be described.

Preparation process A



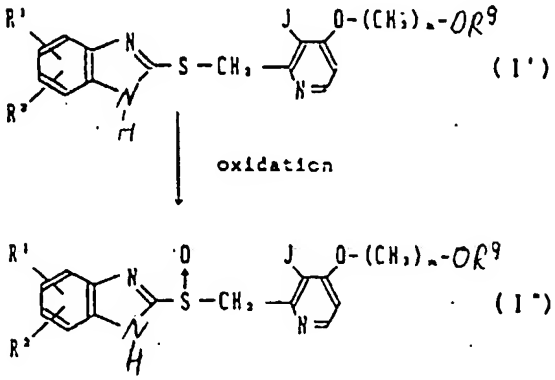
(II)

wherein R^1 and R^2 are as defined above



(III)

wherein m, R^9 and J are as defined above and Y stands for a halogen atom or a sulfonyloxy group



(I') (I")

That is, a compound represented by the general formula (II) is reacted with a halide or sulfonate represented by the general formula (III) to obtain a compound represented by the general formula (I') which is an objective compound of the present invention.

Examples of the halogen atom defined with respect to Y include chlorine, bromine and iodine, while those of the sulfonyloxy group include alkylsulfonyloxy groups such as methylsulfonyloxy and ethylsulfonyloxy groups and aromatic sulfonyloxy groups such as benzenesulfonyloxy and tosyloxy groups.

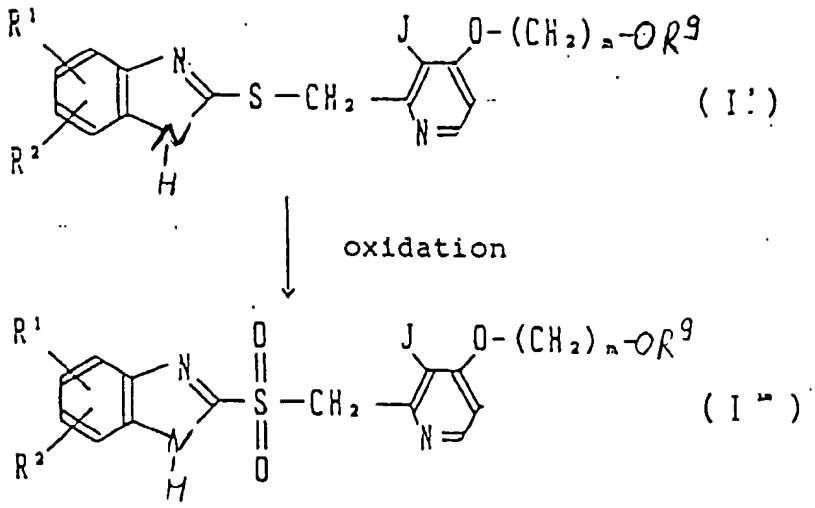
The above reaction is preferably carried out in the presence of an acid scavenger. Examples of the acid scavenger include carbonates and hydrocarbonates of alkali metals, such as potassium carbonate, sodium carbonate and sodium hydrogencarbonate; alkali hydroxides such as sodium hydroxide and potassium hydroxide and organic amines such as pyridine and triethylamine. Examples of the solvent to be used in the reaction include alcohols such as methyl and ethyl alcohols, tetrahydrofuran, dioxane, dimethylformamide, dimethyl sulfoxide and mixtures thereof with water.

The reaction temperature may be from -40°C to the boiling point of the solvent used, preferably from about 0 to 60°C.

The obtained compound (I') can be easily oxidized into its sulfinyl derivative (I") which is an objective compound of the present invention corresponding to a compound of the general formula (I) wherein n is 1.

This oxidation can be carried out according to an ordinary process by the use of an oxidizing agent such as hydrogen peroxide, peracetic acid, m-chloroperbenzoic acid, sodium hypochlorite or sodium hypobromite. The solvent to be used in the oxidation is generally selected from among dichloromethane, chloroform, benzene, toluene, methanol, ethanol and the like. The oxidation temperature may be from -70°C to the boiling point of the solvent used, preferable from -60 to 25°C.

Furthermore, a sulfone derivative which is an objective compound of the present invention corresponding to a compound of the formula (I) wherein n is 2 can be prepared by, for example, the following process:



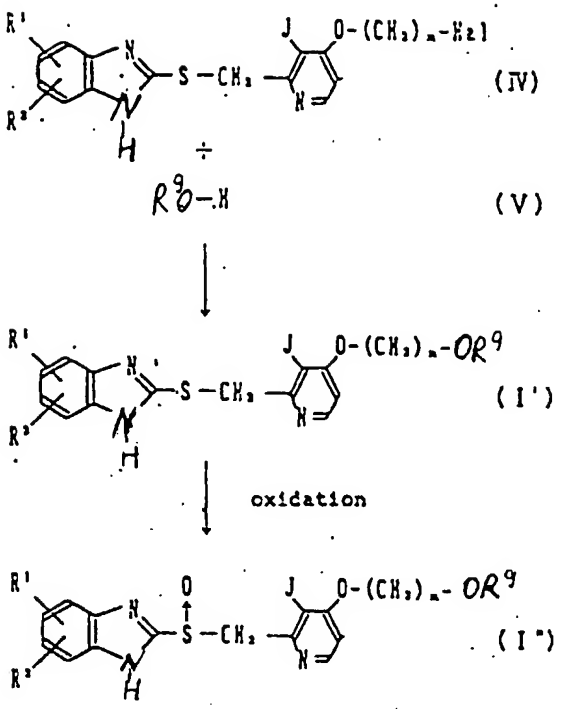
wherein R^1, R^2, J, m and R^9 are as defined above.

That is, the thioether derivative represented by the general formula (I') which is an objective compound of the present invention is oxidized into its sulfone derivative represented by the general formula (I''') which is another objective compound of the present invention.

More precisely, the sulfone derivative (I''') which is an objective compound of the present invention can be prepared by dissolving the compound (I') in a solvent selected from among aromatic hydrocarbons such as benzene, toluene and xylene; halogenated hydrocarbons such as dichloromethane, chloroform and carbon tetrachloride; water; alcohols such as methanol and ethanol; ethyl acetate; acetone; acetic acid and the like to obtain a solution, adding at least twice by equivalent as much oxidizing agent selected from among hydrogen peroxide, peracetic acid, m-chloroperbenzoic acid, sodium hypochlorite, sodium m-periodate and the like to the solution under cooling with ice or at a room temperature and reacting the compound (I') with the oxidizing agent.

Alternatively, the sulfone derivative (I''') can be prepared by dissolving the sulfoxide derivative (I'') obtained by the above process in a solvent such as chloroform, adding an oxidizing agent such as m-chloroperbenzoic acid to the obtained solution and reacting the sulfoxide derivative (I'') with the oxidizing agent.

Preparation process B



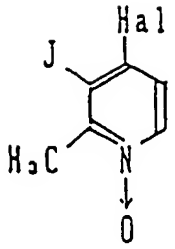
wherein R^1, R^2, m, J, and R^9 are as defined above and Hal stands for a halogen atom.

That is, an objective compound represented by the general formula (I) can be prepared by reacting a halide represented by the general formula (IV) with an alcohol, thiol or amine represented by the general formula: R^9O-H (V). This reaction is preferably carried out in the presence of an acid scavenger. Examples of the acid scavenger include carbonates and hydrogencarbonates of alkali metals, such as potassium carbonate and sodium carbonate; alkali hydroxides such as sodium hydroxide and potassium hydroxide and triethylamine. Examples of the solvent to be used in the reaction include ethers such as tetrahydrofuran and dioxane; ketones such as acetone and methyl ethyl ketone; benzene homologues such as benzene, toluene and xylene; acetonitrile; dimethylformamide; dimethyl sulfoxide and hexamethylphosphoric triamide. The reaction may be carried out either under cooling with ice or at a temperature not exceeding the boiling point of the solvent used.

The obtained compound (I') which is an objective compound of the present invention can be oxidized into its sulfinyl derivative represented by the general formula (I") in a similar manner to that described above in Preparation process A.

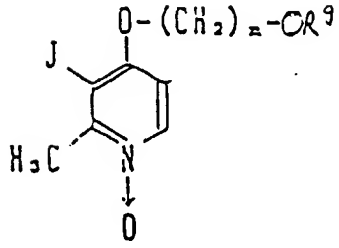
Process for the preparation of starting materials

The compound represented by the general formula (III) to be used in the Preparation process A as a starting material can be prepared by, for example, the following process:



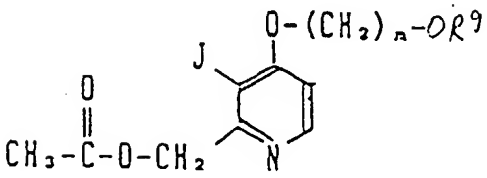
(VIII)

(Step 1) $HO-(CH_2)_n-OR^9$ (IX)



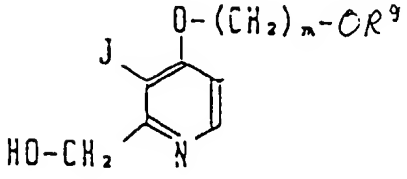
(X)

(Step 2)



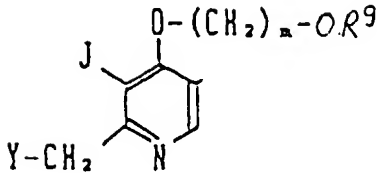
(XI)

(Step 3)



(XII)

(Step 4)



(III)

wherein m, R^9, J, and Y are as defined above.

(Step 1)

A 4-halogenopyridine oxide derivative (VIII) (for example, 4-chloro-2,3-dimethylpyridine 1-oxide) is reacted with an alcohol derivative represented by the general formula (IX) in the presence of a base to obtain an alkoxy derivative represented by the general formula (X).

Examples of the base include alkali metal hydrides such as sodium hydride and potassium hydride; alkali metals such as metallic sodium; sodium alcoholates such as sodium methoxide and alkali metal hydroxides such as sodium hydroxide and potassium hydroxide. This reaction is carried out either in the absence or any solvent or in a solvent selected from among ethers such as tetrahydrofuran and dioxane; ketones such as acetone and methyl ethyl ketone; benzene homologues such as benzene, toluene and xylene; acetonitrile; dimethylformamide; dimethyl sulfoxide; hexamethylphosphoric triamide and the like at a temperature of from one under cooling with ice to the boiling point of the solvent used.

(Step 2)

The alkoxy derivative of the general formula (X) prepared in the Step 1 is heated in acetic anhydride to a temperature of about 60 to 100°C to obtain an acetoxymethylpyridine derivative represented by the general formula (XI).

(Step 3)

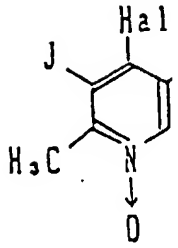
The acetoxymethylpyridine derivative (XI) prepared in the Step 2 is hydrolyzed into the corresponding 2-hydroxymethylpyridine derivative represented by the general formula (XII).

This hydrolysis is generally carried out under alkaline conditions.

(Step 4)

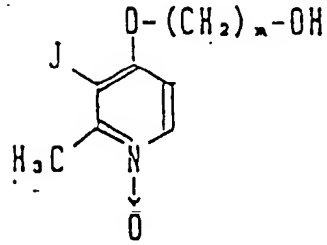
The 2-hydroxymethylpyridine derivative (XII) prepared in the Step 3 is halogenated with, for example, a chlorinating agent such as thionyl chloride into a 2-halogenomethylpyridine derivative represented by the general formula (III). In this halogenation, for example, chloroform or dichloromethane is used as a solvent. Further, the 2-hydroxymethylpyridine derivative (XII) is reacted with an active sulfonyl chloride such as methanesulfonyl chloride to obtain a sulfonyloxy derivative represented by the general formula (III). In this reaction, for example, chloroform, dichloromethane, ether, tetrahydrofuran, pyridine or benzene is used as a solvent.

Alternatively, the compound represented by the general formula (X) to be used in the above process can be prepared by the following process:



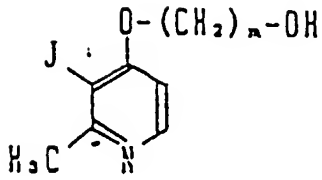
(VIII)

(Step 1) $HO-(CH_2)_n-OH$ (XIII)



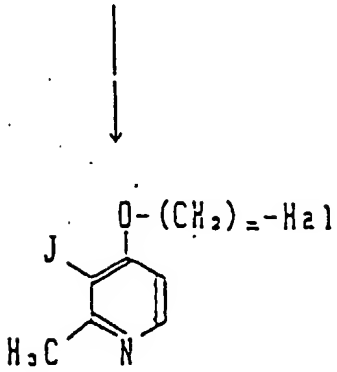
(XIV)

(Step 2)



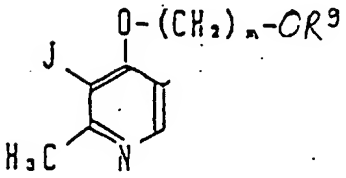
(XV)

(Step 3)



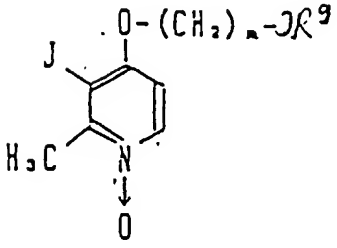
(XII)

(Step 4) R^9OH (V)



(XI)

(Step 5)



(X)

(Step 1)

A compound represented by the general formula (VIII), wherein Hal stands for a halogen atom such as chlorine atom, is condensed with a compound represented by the general formula (XIII) according to an ordinary process to obtain a compound represented by the general formula (XIV).

This condensation is preferably carried out in the presence of a base selected from among alkali metal hydrides

such as sodium hydride and potassium hydride; alkali metals such as metallic sodium; alkali metal hydroxides such as sodium hydroxide and potassium hydroxide and the like.

The condensation is carried out either in the absence of any solvent or in a solvent selected from among ethers such as tetrahydrofuran and dioxane; ketones such as acetone and methyl ethyl ketone; benzene homologues such as benzene, toluene and xylene; acetonitrile; dimethylformamide; dimethyl sulfoxide; hexamethylphosphoric triamide and the like at a temperature suitably selected from the range of one under cooling with ice to the boiling point of the solvent used.

(Step 2)

The obtained alkoxy derivative (XIV) is reduced into the compound (XV). Precisely, the alkoxy derivative (XIV) is hydrogenated in the presence of a 10% palladium/carbon catalyst in an acetic anhydride/acetic acid mixture to obtain the reduction product (XV).

(Step 3)

The obtained compound (XV) is halogenated with, for example, a chlorinating agent such as thionyl chloride to obtain a 2-halogenoethyl derivative represented by the general formula (XVI). In this halogenation, for example, chloroform or dichloromethane is used as a solvent.

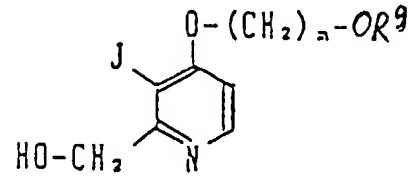
(Step 4)

The obtained compound (XVI) is reacted with an alcohol, thiol or amine represented by the general formula (V) to obtain a compound represented by the general formula (XVII). This reaction is preferably carried out in the presence of an acid scavenger as in the reaction of the Preparation process B.

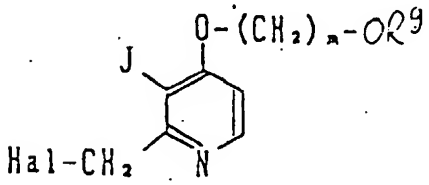
(Step 5)

The obtained compound (XVII) is oxidized with an oxidizing agent such as hydrogen peroxide, peracetic acid or m-chloroperbenzoic acid to obtain the corresponding N-oxide derivative.

Alternatively, the compound represented by the general formula (III) to be used in the Preparation process A as a starting material can be prepared by the following process:



(XII)



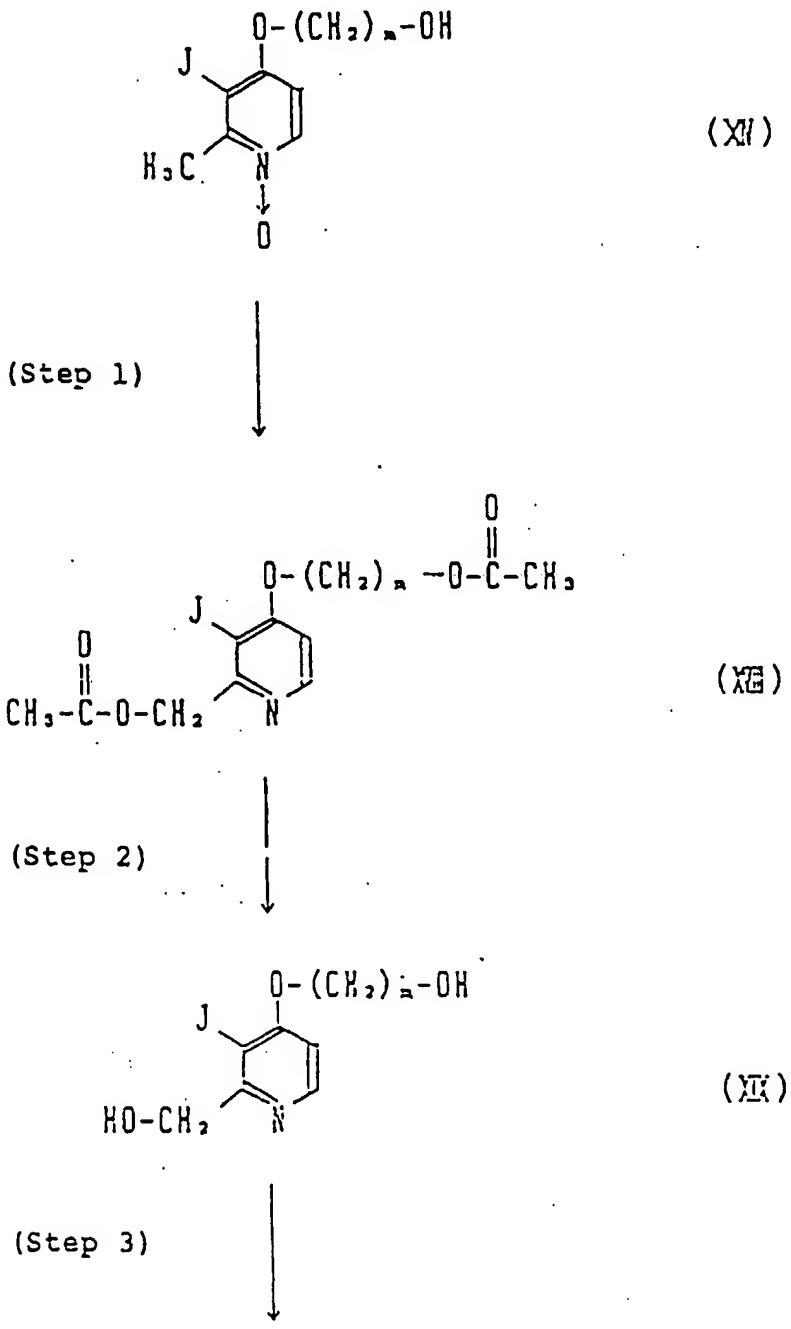
(III)

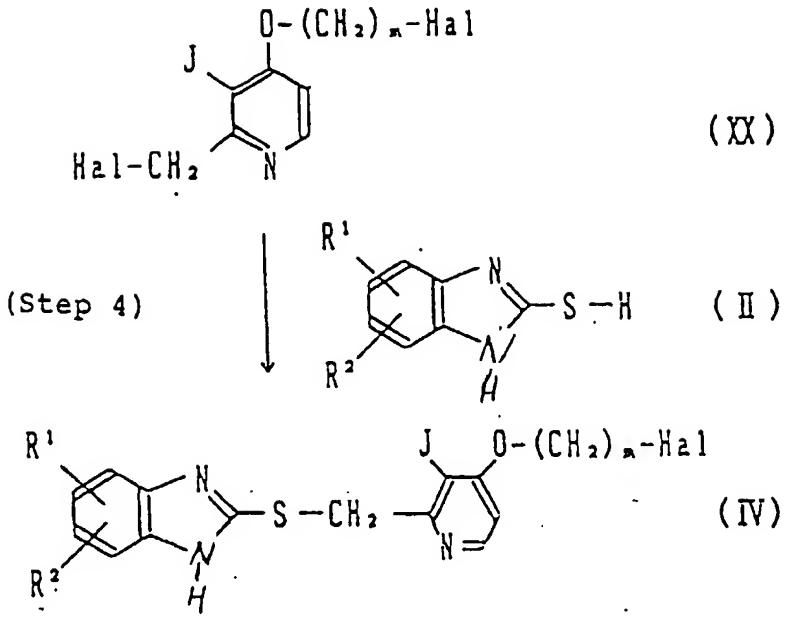
wherein Hal stands for a halogen atom and R^9 and m are as defined above.

A compound represented by the general formula (XII) is halogenated with, for example, a chlorinating agent such as thionyl chloride at a temperature of 0°C to a room temperature to obtain a halogenomethylpyridine derivative rep-

resented by the general formula (III). In this halogenation, for example, chloroform or dichloromethane is used as a solvent.

The compound (IV) to be used in the Preparation process B as a starting material can be prepared by, for example, the following process:





wherein Hal stands for a halogen atom and the others are as defined above.

(Step 1)

A compound represented by the general formula (XIV) is converted into the corresponding acetylate (XVIII) according to an ordinary process. For example, acetic anhydride or acetyl chloride is used in this reaction.

(Step 2)

The obtained acetylate is hydrolyzed in the pressence of an acid or a base to obtain the corresponding diol derivative (XIX).

(Step 3)

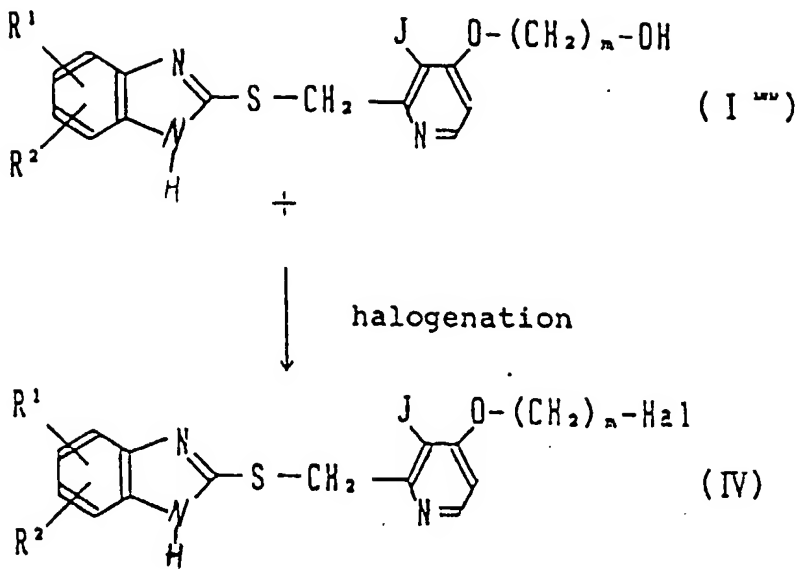
The diol derivative (XIX) is halogenated with, for example, a chlorinating agent such as thionyl chloride to obtain a dihalide represented by the general formula (XX). In this halogenation, for example, chloroform or dichloromethane is used as a solvent.

(Step 4)

The obtained dihalide (XX) is reacted with a compound represented by the general formula (II) to obtain a sulfide derivative represented by the general formula (IV).

This reaction is carried out in the presence of an acid scavenger selected from among carbonates and hydrogencarbonates of alkali metals, such as potassium carbonate and sodium carbonate, and alkali hydroxides such as sodium hydroxide and potassium hydroxide. Examples of the solvent to be used in the reaction include alcohols such as ethanol and methanol, tetrahydrofuran, dioxane, dimethylformamide, dimethyl sulfoxide and mixtures thereof with water. The reaction temperature may be from 0°C to the boiling point of the solvent used, preferably from about 40 to 60°C.

Alternatively, the compound (IV) to be used in the Preparation process B as a starting material can be prepared by the following process:



wherein Hal stands for a halogen atom and the others are as defined above.

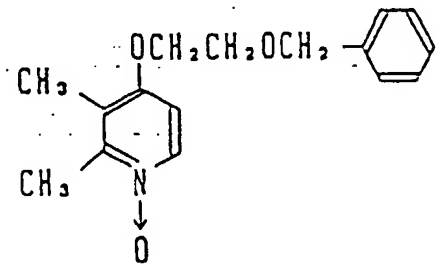
That is, the compound (IV) can be obtained by halogenating the compound (I"") which is an objective compound of the present invention and prepared by the Preparation process A according to an ordinary process. More precisely, a compound represented by the general formula (I"") is halogenated with, for example, a chlorinating agent such as thionyl chloride to obtain a halide represented by the general formula (IV). In this halogenation, chloroform or dichloromethane 15 preferably used as a solvent and the reaction temperature ranges preferably from a room temperature to about 80°C.

Examples of the present invention will now be described, though it is needless to say that the present invention is not limited by them at all.

The following Preparative Examples refer to the preparation of raw materials to be used in the preparation of the objective compounds according to the present invention.

Preparative Example 1

Synthesis of 4-(2-benzyloxyethoxy)-2,3-dimethylpyridine N-oxide

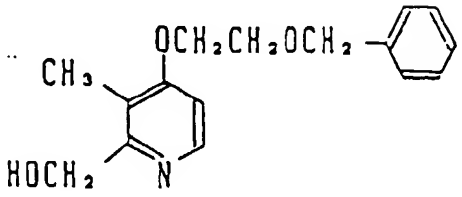


1.82 g (79.13 mmol) of Na was added to 50 ml of benzyloxyethanol to obtain a mixture. This mixture was stirred at 50°C for 2 hours. 5.0 g (31.76 mmol) of 4-chloro-2,3-dimethylpyridine N-oxide was added to the resulting mixture at a room temperature. The obtained mixture was stirred at 110°C for 1.5 hours, cooled to a room temperature and filtered to remove insoluble matter. The filtrate was adsorbed to silica gel with dichloromethane. The silica gel was treated with 5 to 30% ethyl acetate in hexane to elute benzyloxyethanol. Then, the resulting silica gel was treated with 5 to 30% methanol in ethyl acetate to obtain 7.15 g of 4-(2-benzyloxyethoxy)-2,3-dimethylpyridine N-oxide as an oil.

^{1}H-NMR($CDCl_3$) δ ;2.20(s,3H), 2.47(s,3H), 3.8~4.0(m,2H), 4.1~4.25(m,2H), 4.6 (s, 2H), 6.65(d,J = 7.03Hz,1H), 7.33(s,5H), 8.12(d,J = 7.03Hz,1H)

Preparative Example 2

Synthesis of 4-(2-benzyloxyethoxy)-2-hydroxymethyl-3-methylpyridine

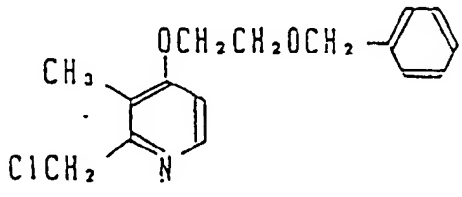


A mixture comprising 6.5 g of 4-(2-benzyloxyethoxy-2,3-dimethylpyridineN-oxide and 56 ml of acetic anhydride was stirred at 80 to 90°C for one hour and distilled to remove the acetic anhydride. The obtained residue was made weakly basic with an aqueous solution of sodium carbonate and extracted with methyl ethyl ketone. The extract was dried over magnesium sulfate and distilled to remove the methyl ethyl ketone. Thus, 7.0 g of 2-acetoxymethyl-4-(2-benzyloxyethoxy)-3-methylpyridine was obtained. This intermediate was dissolved in 90 ml of ethanol, followed by the addition of 1.43 g of sodium hydroxide. The obtained mixture was stirred at 40°C for one hour, followed by the addition of water. The mixture was extracted with methyl ethyl ketone. The obtained extract was dried over magnesium sulfate to obtain 5.4 g of 4-(2-benzyloxyethoxy)-2-hydroxymethyl-3-methylpyridine.

^{1}H-NMR($CDCl_3$) δ ;2.06(s,3H), 3.7~3.95(m, 2H), 4.0~4.3(m,2H), 4.6(s,4H), 6.70(d, J=6.7Hz,1H), 7.33(s,5H), 8.27 (d,J = 6.7 Hz,1H)

Preparative Example 3

Synthesis of 4-(2-benzyloxyethoxy)-2-chloromethyl-3-methylpyridine

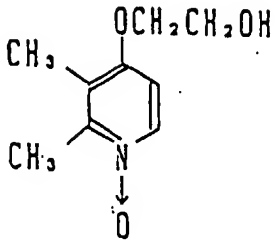


5.3 g of 4-(2-benzyloxyethoxy)-2-hydroxymethyl-3-methylpyridine was dissolved in 60 ml of chloroform to obtain a solution. A solution of 5.8 g of thionyl chloride in 40 ml of chloroform was dropwise added to the above solution under cooling with ice. The obtained mixture was stirred at a room temperature for 7 hours and distilled under a reduced pressure to obtain a residue. 200 ml of a 2N aqueous solution of sodium carbonate was added to the residue. The obtained mixture was extracted with chloroform and the extract was dried over magnesium sulfate and distilled to remove the chloroform. 6.3 g of the title compound was obtained.

^{1}H-NMR($CDCl_3$) δ ; 2.27(s,3H), 3.5~4.25(m, 4H), 4.56(s,2H), 4.66(s,2H), 6.7(d,J = 5.71Hz,1H), 7.30(s,5H), 8.27 (d,J = 5.71Hz, 1H)

Preparative Example 4

4-(2-Hydroxyethoxy)-2,3-dimethylpyridine N-oxide



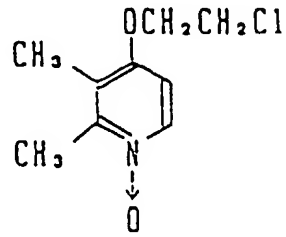
4.60 g (0.2 mol) of metallic sodium was dissolved in 80 ml of ethylene glycol under cooling with ice to obtain a solution. This solution was stirred in a nitrogen atmosphere at 100°C for one hour, followed by the addition of 15.76 g (0.1 mol) of 4-chloro-2,3-dimethylpyridine N-oxide at a room temperature. The obtained mixture was stirred at 120°C for 2 hours. After the completion of the reaction, the reaction mixture was distilled to dryness to remove the ethylene glycol. The obtained residue was purified by silica gel column chromatography (solvent: chloroform/methanol = 19 : 1) to obtain 13.28 g of 4-(2-hydroxyethoxy)-2,3-dimethylpyridine N-oxide as a white crystal.

^{1}H-NMR(CD_3OD) δ;

2.29(s,3H), 2.55(s,3H), 3.93(t,2H), 4.20 (t,2H), 7.04(d,H), 8.18(d,H)

Preparative Example 5

4-(2-Chloroethoxy)-2,3-dimethylpyridine N-oxide



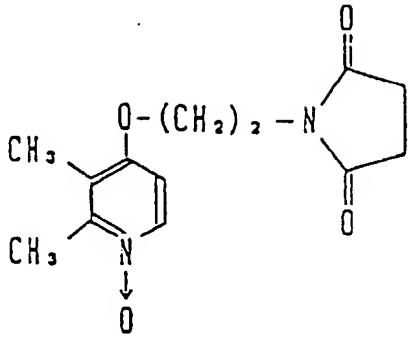
1.0 ml of thionyl chloride was gradually added to a solution of 0.92 g (5 mmol) of 4-(2-hydroxyethoxy)-2,3-dimethylpyridine N-oxide in 10 ml of chloroform under cooling with ice. The obtained mixture was heated under reflux for 2 hours, cooled by allowing to stand, neutralized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with 100 ml of methyl ethyl ketone twice. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography (solvnet: chloroform/methanol = 19 : 1) to obtain 0.56 g of 4-(2-chloroethoxy)-2,3-dimethylpyridine N-oxide as a colorless crystal.

^{1}H-NMR($CDCl_3$) δ;

2.24(s,3H), 2.54(s,3H), 3.86(t,2H), 4.28 (t,2H), 6.62(d,H), 8.17(d,H)

Preparative Example 6

2,3-Dimethyl-4-(2-succinimidoethoxy)pyridine N-oxide



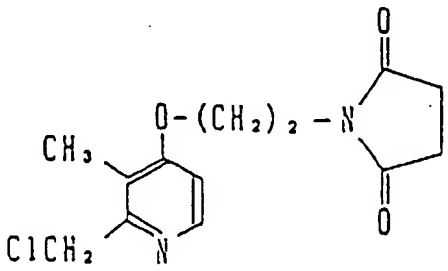
A mixture comprising 0.40 g (2 mmol) of 4-(2-chloroethoxy)-2,3-dimethylpyridine N-oxide, 0.30 g (3 mmol) of succinimide, 0.48 g (3.5 mmol) of potassium carbonate and 30 ml of methyl ethyl ketone was heated under reflux for 2 hours, cooled by allowing to stand and filtered. The filtrate was evaporated to dryness to remove the methyl ethyl ketone. The obtained residue was purified by silica gel column chromatography (solvent: $CHCl_3$/MeOH = 19 : 1) to obtain 0.12 g of 2,3-dimethyl-4-(2-succinimidoethoxy)pyridine N-oxide as a white crystal.

^{1}H-NMR($CDCl_3$) δ;

2.12(s,3H), 2.49(s,3H), 2.73(s,4H), 3.80~4.25(m,4H), 6.51(d,H), 8.03(d,H)

Preparative Example 7

2-Chloromethyl-3-methyl-4-(2-succinimidoethoxy) pyridine



0.12 g of 2,3-dimethyl-4-(2-succinimidoethoxy)-pyridine N-oxide was dissolved in 5 ml of acetic anhydride to obtain a solution. This solution was stirred at 100°C for 0.5 hour and cooled, followed by the addition of 30 ml of ethanol. The obtained mixture was stirred at a room temperature for 0.5 hour and distilled to remove the solvent. Thus, 0.14 g of crude 2-acetoxymethyl-3-methyl-4-(2-succinimidoethoxy)-pyridine was obtained as an oil.

^{1}H-NMR($CDCl_3$) δ;

2.10(s,3H), 2.14(s,3H), 2.72(s,4H), 3.72~4.24(m,4H), 5.15(s,2H), 6.61(d,H), 8.24 (d,H)

This acetoxymethyl derivative was dissolved as such in 5 ml of 1 N HCl to obtain a solution. This solution was stirred at 100°C for 0.5 hour, cooled, neutralized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with 100 ml of chloroform twice. The obtained extract was dried over magnesium sulfate and filtered. The filtrate was concentrated to obtain 0.12 g of crude 2-hydroxymethyl-3-methyl-4-(2-succinimidoethoxy)pyridine as a colorless crystal.

^{1}H-NMR($CDCl_3$) δ;

1. 93 (s, 3H), 2. 68 (s, 4H), 3. 80~4.22(m, 4H), 4. 56 (s, 2H), 6. 59 (d, H), 8. 21 (d, H)

This crude hydroxymethyl derivative was dissolved as such in 5 ml of chloroform to obtain a solution. 0.11 g of thionyl chloride was dropwise added to this solution under cooling with ice. The obtained mixture was heated under

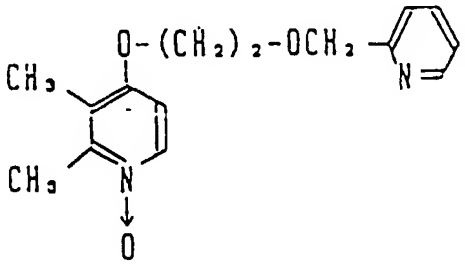
reflux for 0.5 hour, cooled, neturalized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with 100 ml of chloroform twice. The obtained extract was dried over magnesium sulfate and filtered. The filtrate was concentrated and dried in a vacuum to obtain 0.07 g of 2-chloromethyl-3-methyl-4-(2-succinimidoethoxy)pyridine as a white semicrystal.

^{1}H-NMR($CDCl_3$) δ;

2.15(s,3H), 2.68(s,4H), 3.80~4.20(m,4H), 4.60(s,2H), 6.61(d,H), 8.22(d,H)

Preparative Example 8

2,3-Dimethyl-4-(2-pyridylmethoxyethoxy)pyridine N-oxide



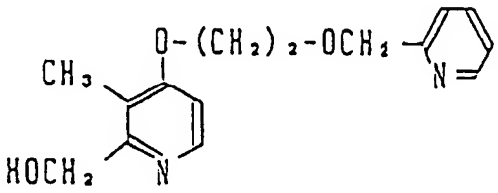
0.39 g of 60% sodium hydride was added to a suspension of 1.20 g (6.5 mmol) of 4-(2-hydroxyethoxy)-2,3-dimethylpyridine N-oxide in 40 ml of tetrahydrofuran under cooling with ice in a nitrogen atmosphere to obtain a mixture. This mixture was stirred for 0.5 hour, followed by the addition of 0.83 g (6.5 mmol) of 2-chloromethylpyridine. The obtained mixture was heated under reflux for 8 hours, cooled and filtered. The filtrate was concentrated and purified by silica gel column chromatography (solvent: ethyl acetate/n-hexane = 4 : 1 ~ $CHCl_3$/MeOH = 19 : 1) to obtain 0.61 g of 2,3-dimethyl-4-(2-pyridylmethoxyethoxy)pyridine N-oxide.

^{1}H-NMR($CDCl_3$) δ;

2.20(s,3H), 2.50(s,3H), 3.80~4.04(m,2H), 4.04~4.28(m,2H), 4.70(s,2H), 6.60(d,H), 7.00~7.74(m,3H), 8.04(d,H), 8.45(d,H)

Preparative Example 9

2-Hydroxymethyl-3-methyl-4-(2-pyridylmethoxyethoxy)pyridine

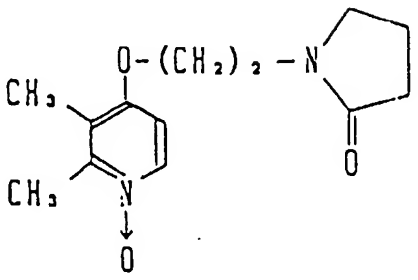


A mixture comprising 0.60 g of 2,3-dimethyl-4-(2-pyridylmethoxyethoxy)pyridine N-oxide and acetic anhydride was stirred at 100°C for 0.5 hour and cooled, followed by the addition of 40 ml of ethanol. The obtained mixture was stirred at a room temperature for 0.5 hour and distilled to remove the solvent. The residue was dried in a vacuum to obtain 0.47 g of crude 2-acetoxymethyl-3-methyl-4-(2-pyridylmethoxyethoxy)pyridine as an oil.

This crude intermediate was dissolved as such in 1N HCl to obtain a solution. This solution was stirred at 100°C for one hour, cooled, neutralized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with 50 ml of dichloromethane twice. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography (solvent: ehtyl acetate) to obtain 0.40 g of 2-hydroxymethyl-3-methyl-4-(2-pyridylmethoxyethoxy)pyridine as a colorless semicrystal.

Preparative Example 10

2,3-Dimethyl-4-[2-(2-pyrrolidone)ethoxy]pyridine N-oxide



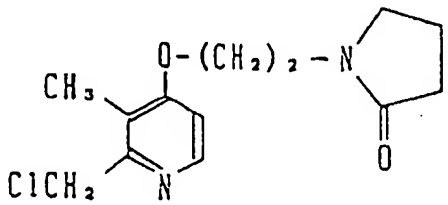
0.42 g of sodium hydride was added to 30 cc of N,N-dimethylformamide at a room temperature to obtain a mixture. This mixture was cooled to 0°C, followed by the addition of 0.74 g of 2-pyrrolidone. The obtained mixture was stirred at 80°C for 1.5 hours and cooled to a room temperature, followed by the addition of 1.17 g of 4-(2-chloroethoxy)-2,3-dimethylpyridine N-oxide. The obtained mixture was stirred at 60 to 80°C for 5 hours and cooled, followed by the addition of 20 cc of a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was extracted with chloroform. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated to obtain a crude product. This crude product was purified by silica gel column chromatography to obtain 430 mg of 2,3-dimethyl-4-[2-(2-pyrrolidone)-ethoxy]pyridine N-oxide as a yellow crystal.

^{1}H-NMR($CDCl_3$) δ;

2.2(s,3H), 2.54(s,3H), 1.9~2.5(m,4H), 3.57(t,J=7Hz,2H), 3.73(t,J=6Hz,2H), 4.16 (t,J=6Hz,2H), 6.65(d,J = 7Hz,1H), 8.15(d,J = 7Hz,1H)

Preparative Example 11

2-Chloromethyl-3-methyl-4-[2-(2-pyrrolidone)ethoxy]pyridine



10 cc of acetic anhydride was added to 0.65 g of 2,3-dimethyl-4-[2-(2-pyrrolidone)ethoxyl N-oxide at a room temperature to obtain a mixture. This mixture was stirred at 90°C for 2 hours, followed by the addition of ethanol. The obtained mixture was distilled under a reduced pressure to obtain 0.79 g of crude 2-acetoxymethyl-3-methyl-4-[2-(2-pyrrolidone)ethoxy]pyridine.

20 cc of 1N HCl was added to this crude intermediate to obtain a mixture. This mixture was stirred at 100°C for 2 hours, cooled, neutralized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with chloroform. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled under a reduced pressure to obtain 510 mg of crude 2-hydroxymethyl-3-methyl-4-[2-(2-pyrrolidone)ethoxy]pyridine as an ocherous crystal.

^{1}H-NMR($CDCl_3$) δ;

2.04(s,3H), 1.9~2.6(m,4H), 3.58(t,J = 7Hz,2H), 3.73(t,J = 6Hz,2H), 4.2(t,J = 6Hz,2H), 4.65(s,2H), 6.7(d,J =7Hz,1H), 8.3(d,J = 7Hz, 1H)

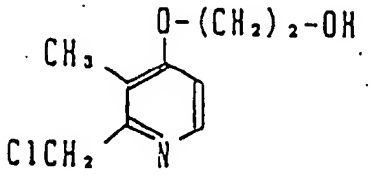
500 mg of this crude intermediate was dissolved in 10 ml of dichloromethane to obtain a solution. 1.19 g of thionyl chloride was dropwise added to this solution at -20°C. The obtained mixture was stirred at a room temperature for 30 minutes, neutralized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with chloroform. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled under a reduced pressure to obtain 0.57 mg of crude 2-chloromethyl-3-methyl-4-[2-(2-pyrrolidone)ethoxy]pyridine as an oil.

^{1}H-NMR($CDCl_3$) δ;

2.25(s,3H), 1.8~2.5(m,4H), 3.54(t,J = 7Hz,2H), 3.68(t,J =6Hz,2H), 4.1(t,J=6Hz,2H), 6.62(d,J = 6Hz,1H), 8.22(d,J = 6Hz,1H)

Preparative Example 12

2-Chloromethyl-4-(2-hydroxyethoxy)-3-methylpyridine



15 ml of acetic anhydride was added to 25 g of 4-(2-hydroxyethoxy)-2,3-dimethylpyridine N-oxide to obtain a solution. This solution was stirred at 90°C for 2 hours, followed by the addition of ethanol. The obtained mixture was distilled under a reduced pressure to obtain 4-(2-acetoxyethoxy)-2-acetoxymethyl-3-methylpyridine.

20 g of sodium hydroxide, 20 ml of water and 50 ml of ethanol were added to this intermediate to obtain a mixture. This mixture was stirred at a room temperature for 10 minutes and distilled to remove the ethanol, followed by the addition of 50 ml of a saturated aqueous solution of common salt. The obtained mixture was extracted with 2-butanone. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled under a reduced pressure to obtain 20 g of 4-(2-hydroxyethoxy)-2-hydroxymethyl-3-methylpyridine.

^{1}H-NMR($CDCl_3$) δ ;

2.02(s,3H), 3.9~4.2(m,4H), 4.50(s,2H), 6.63(d,J = 6Hz,1N), 8.15(d,J = 6Hz,1H)

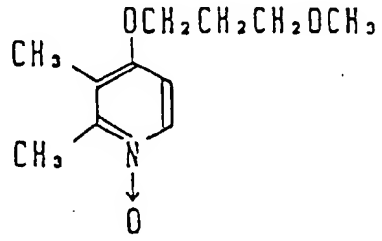
11.9 g of the 4-(2-hydroxyethoxy)-2-hydroxymethyl-3-methylpyridine prepared above was dissolved in 200 ml of dichloromethane to obtain a solution. 24 ml of thionyl chloride was dropwise added to this solution at 0°C. The obtained mixture was stirred at a room temperature for 2 hours and distilled under a reduced pressure to remove the dichloromethane and excess thionyl chloride. A saturated aqueous solution of sodium hydrogencarbonate was added to the residue to obtain a mixture. This mixture was extracted with chloroform. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated to obtain 10.9 g of 2-chloromethyl-4-(2-hydroxyethoxy)-3-methylpyridine.

^{1}H-NMR($CDCl_3$) δ ;

2.3(s,3H), 3.9~4.2(m,4H), 4.69(s,2H), 6.73(d,J = 6Hz,1H), 8.3(d,J =6Hz,1H)

Preparative Example 13

4-(3-Methoxypropoxy)-2,3-dimethylpyridine N-oxide



2. 0 g (22 mmol) of 3-methoxypropanol was dissolved in 50 ml of dimethyl sulfoxide to obtain a solution. 2. 7 g (66 mmol) of sodium hydride was added to this solution at a room temperature. The obtained mixture was stirred at 60°C for one hour and cooled to a room temperature by allowing to stand, followed by the addition of 3.0 g (19 mmol) of 4-chloro-2,3-dimethylpyridine N-oxide. The obtained mixture was stirred at 40°C for one hour. After the completion of the reaction, the reaction mixture was distilled to remove the dimethyl sulfoxide. The obtained residue was purified by silica gel column chromatography to obtain 760 mg of 4-(3-methoxypropoxy)-2,3-dimethylpyridine N-oxide.

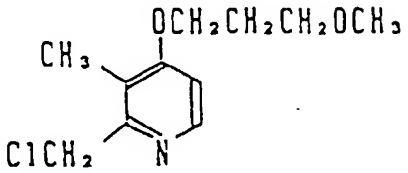
^{1}H-NMR($CDCl_3$) δ;

2.1 (m,2H), 2.2(s,3H), 2.54(s,3H), 3.35(s,3H), 3.55(t,J = 6Hz,2H), 4.1 (t,J = 6Hz,2H), 6.65(d,J = 7.4Hz,1H), 8.16(d,J

= 7.4Hz,1H)

Preparative Example 14

2-Chloromethyl-4-(3-methoxypropoxy)-3-methylpyridine



20 ml of acetic anhydride was added to 760 mg (3. 6 mmol) of 4-(3-methoxypropoxy)-2,3-dimethylpyridine N-oxide to carry out the reaction at 90°C for one hour. The reaction mixture was distilled to remove the acetic anhydride, followed by the addition of a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was extracted with chloroform. The extract was concentrated to obtain 700 mg of 2-acetoxymethyl-4-(3-methoxypropoxy)-3-methylpyridine as a brown oil.

500 mg of sodium hydroxide and 15 cc of ethanol were added to the 2-acetoxymethyl-4-(3-methoxypropoxy)-3-methylpyridine prepared above. The obtained mixture was stirred at 50°C for one hour. After the completion of the reaction, the reaction mixture was distilled to remove the ethanol, followed by the addition of water. The obtained mixture was extracted with chloroform. The obtained chloroform layer was concentrated to obtain 450 mg of 2-hydroxymethyl-4-(3-methoxypropoxy)-3-methylpyridineas a brown oil.

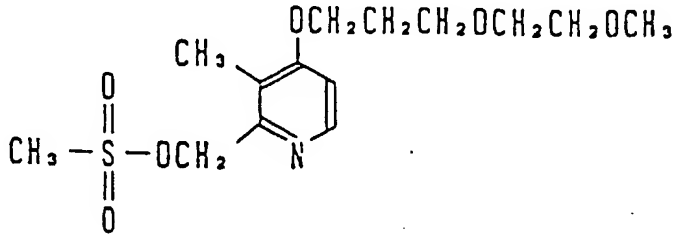
^{1}H-NMR($CDCl_3$) δ ;
2.04(s,3H), 2.1 (m,2H), 3.35(s,3H), 3.56(t, J=5.7Hz,2H), 4.12(t,J =5.7Hz,2H), 4.64(s, 2H), 6.7(d,J=7Hz,1H), 8.24(d,J = 7Hz,1 H)

450 mg of the 2-hydroxymethyl-4-(3-methoxypropoxy)-3-methylpyridineprepared above was dissolved in 20 ml of dichloromethane to obtain a solution. 760 mg of thionyl chloride was dropwise added to this solution at 0°C. The obtained mixture was stirred at a room temperature for 2 hours. After the completion of the reaction, the reaction mixture was distilled to remove the dichloromethane and the thionyl chloride. A saturated aqueous solution of sodium hydrogencarbonate was added to the obtained residue. The obtained mixture was extracted with chloroform. The obtained chloroform layer was concentrated to obtain 470 mg of 2-chloromethyl-4-(3-methoxypropoxy)-3-methylpyridine as a brown crystal.

^{1}H-NMR($CDCl_3$) δ ;
2.1(m,2H), 2.27(s,3H), 3.36(s,3H), 3.56(t, J=5.7Hz,2H), 4.12(t,J=5.7Hz,2H), 4.69(s, 2H), 6.71(d,J=7Hz,1H), 8.26(d,J = 7Hz,1H)

Preparative Example 15

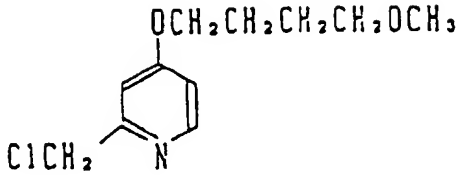
[4-{3-(2-Methoxyethoxy)propoxy}-3-methylpyridine-2-yl]methyl methanesulfonate



2.24 g of triethylamine and 1.27 g of methanesulfonyl chloride were added to a solution of 1.4 g of crude 2-hydroxy-4-{3-(2-methoxyethoxy)}-3-methylpyridine in dichloromethane at -30°C to obtain a mixture. This mixture was brought to a room temperature, followed by the addition of a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was stirred for 30 minutes and extracted with chloroform. The extract was dried over magnesium sulfate and distilled under a reduced pressure to remove the chloroform. 1.9 g of a crude red oil was obtained.

Preparative Example 16

2-Chloromethyl-4-(4-methoxybutoxy)pyridine

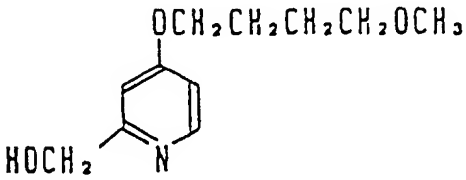


5.6 g of crude 2-hydroxymethyl-4-(4-methoxybutoxy)-pyridine was dissolved in 80 ml of chloroform to obtain a solution. A solution of 3.8 g of thionyl chloride in 10 ml of chloroform was dropwise added to this solution at 0°C. The obtained mixture was stirred at 0°C for one hour. After the completion of the reaction, the reaction mixture was neutralized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with 200 ml of chloroform twice. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled to remove the solvent. The obtained residue was dried in a vacuum to obtain 5.09 g of the title compound as a crude oil.

^{1}H-NMR($CDCl_3$) δ ; 1.55~2.05(m,4H), 3.35(s, 3H), 3.38~3.53(m,2H), 3.91~4.17(m, 2H), 4.61(s,2H), 6.53~7.01 (m,2H), 8.36(d,J = 6.2Hz,1H)

Preparative Example 17

2-Hydroxymethyl-4-(4-methoxybutoxy)pyridine

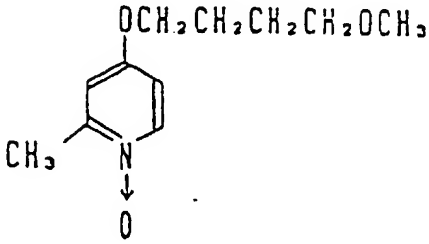


5.06 g (0.024 mol) of 4-(4-methoxybutoxy)-2-methylpyridine 1-oxide was dissolved in 80 ml of acetic anhydride to obtain a solution. This solution was stirred at 100°C for one hour, cooled and distilled to remove the solvent. 150 ml of 1N hydrochloric acid was added to the residue. The obtained mixture was stirred at 100°C for one hour, cooled, neutralized with sodium hydrogencarbonate and extracted with 200 ml of chloroform twice. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled to remove the solvent and the residue was dried in a vacuum to obtain 5.66 g of the title compound as a crude oil.

^{1}H-NMR($CDCl_3$) δ ; 1.58~2.08(m,4H), 3.32~3.54(m,2H), 3.34(s,3H), 3.82~4.16(m, 2H), 4.69(s,2H), 5.02(s, 1H)), 6.54~6.88 (m,2H), 8.30(d,J = 6.2Hz,1H)

Preparative Example 18

4-(4-Methoxybutoxy)-2-methylpyridine 1-oxide



6.77 g (0.065 mol) of 4-methoxybutanol was dissolved in 60 ml of dimethyl sulfoxide to obtain a solution. 2.6 g (0.065 mol) of 60% sodium hydride was added to this solution at a room temperature in a nitrogen atmosphere. The obtained mixture was heated to 60°C, stirred for one hour and cooled to a room temperature. A solution of 4.66 g (0.032 mol) of 4-chloro-2-methylpyridine 1-oxide in 20 ml of dimethyl sulfoxide was dropwise added to the resulting mixture. The obtained mixture was stirred at 40°C for one hour. After the completion of the reaction, 5 ml of water was added to the mixture and the obtained mixture was evaporated to dryness to remove the solvent. 150 ml of water was added to the residue. The obtained mixture was extracted with 200 ml of chloroform four times. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled to remove the solvent. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to obtain 5.06 g of the title compound as an oil.

^{1}H-NMR($CDCl_3$) δ; 1.54~2.07(m,4H), 2.52(s, 3H), 3.36(s,3H), 3.44(t,J =6.2Hz,2H), 4.01(t,J=6.2Hz,2H), 6.60~6.84(m,2H), 8.14(d,J = 5.3Hz,1H)

Preparative Example 19

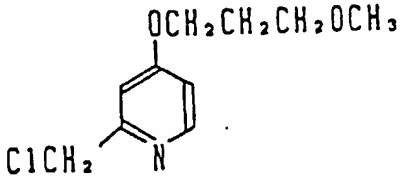
4-Methoxybutanol $CH_3OCH_2CH_2CH_2CH_2OH$

27.04 g (0.3 mol) of 1,4-butanediol was dissolved in 150 ml of tetrahydrofuran to obtain a solution. 7.2 g (0.18 mol) of 60% sodium hydride was added to this solution at 0°C in a nitrogen atmosphere. The obtained mixture was heated under reflux for one hour and cooled to 0°C. 21.73 g (0.15 mol) of 98% methyl iodide was dropwise added to the resulting mixture. The obtained mixture was stirred at a temperature of 30°C or below for 1.5 hours. After the completion of the reaction, the reaction mixture was filtered. The filtrate was distilled to remove the solvent. 200 ml of water was added to the residue and the obtained mixture was washed with 200 ml of n-hexane and extracted with 200 ml of chloroform four times. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled to remove the solvent. 14.5 g of the title compound was obtained.

^{1}H-NMR($CDCl_3$) δ ; 1.54~1.80(m,4H), 1.71(s, 1H), 3.32(s,3H), 3.34~3.73(m,4H)

Preparative Example 20

2-Chloromethyl-4-(3-methoxypropoxy)pyridine

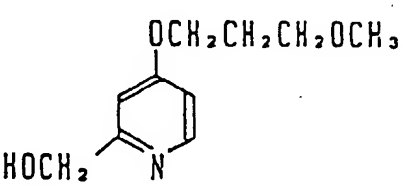


A solution of 2.60 g (0.022 mol) of thionyl chloride in 10 ml of chloroform was dropwise added to a solution of 3.64 g (0.018 mol) of 2-hydroxymethyl-4-methoxypropoxypyridine in 60 ml of chloroform under cooling with ice. The obtained mixture was stirred for one hour, neutralized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with chloroform. The chloroform layer was dried over magnesium sulfate and filtered. The filtrate was concentrated under a reduced pressure to obtain 3.23 g of the title compound as a crude product.

^{1}H-NMR($CDCl_3$) δ ; 1.80~2.20(m,2H), 3.31(s, 3H), 3.49 ((t,J=6.2Hz,2H), 4.07 (t,J=6.2 Hz,2H), 4.55(s,2H), 6.52~6.96(m,2H), 8.26(d,J =5.3Hz,1H)

Preparative Example 21

2-Hydroxymethyl-4-(3-methoxypropoxy)pyridine

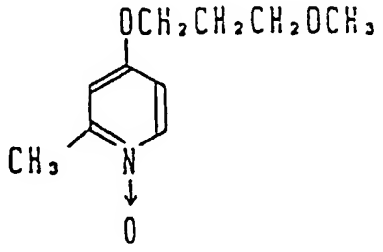


4.05 g (0.02 mol) of 4-methoxypropoxy-2-methylpyridine 1-oxide was dissolved in 50 ml of acetic anhydride to obtain a solution. This solution was stirred at 90°C for 0.5 hour and cooled, followed by the addition of ethanol. The obtained mixture gas concentrated under a reduced pressure, followed by the addition of 150 ml of 1N hydrochloric acid. The obtained mixture was stirred at 100°C for one hour, cooled, neutralized with sodium hydrogencarbonate and extracted with chloroform. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled to remove the solvent. Thus, 3.64 g of the title compound was obtained as a crude product.

^{1}H-NMR($CDCl_3$) δ ; 1.83~2.20(m,2H), 3.30(s, 3H), 3.49((t,J=5.3Hz,2H), 4.05(t,J=5.3Hz,2H), 4.64(s,2H), 4.70(s, 1H), 6.48~6.86(m,2H), 8.21(d,J = 6.2Hz,1H)

Preparative Example 22

4-(3-Methoxypropoxy)-2-methylpyridine 1-oxide

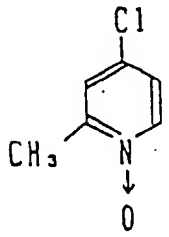


5.85 g (0.065 mol) of methoxypropanol was dissolved in 60 ml of dimethyl sulfoxide to obtain a solution. 2.6 g (0.065 mol) of sodium hydride was added to this solution at a room temperature in a nitrogen atmosphere. The obtained mixture was stirred at 60°C for 0.5 hour. A solution of 4.66 g (0.0325 mol) of 4-chloro-2-methylpyridine 1-oxide in 20 ml of dimethyl sulfoxide was dropwise added to the mixture under cooling with ice. The mixture was stirred at 40°C for one hour. After the completion of the reaction, the reaction mixture was concentrated under a reduced pressure to obtain a solid. 200 ml of water was added to this solid. The obtained mixture was extracted with chloroform and the obtained extract was dried over magnesium sulfate and filtered. The filtrate was concentrated under a reduced pressure and purified by silica gel column chromatography (ethyl acetate/methanol) to obtain 4.09 g of the title compound.

^{1}H-NMR($CDCl_3$) δ; 1.80~2.24(m,2H), 2.48(s, 3H), 3.31(s,3H), 3.48(t,J=6.3Hz,2H), 4.02(t,J=6.3Hz,2H), 6.50~6.78(m,2H), 8.04(d,J = 7.2Hz,1H)

Preparative Example 23

4-Chloro-2-methylpyridine 1-oxide

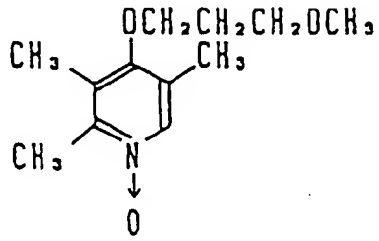


15.4 g (0.1 mol) of 2-methyl-4-nitropyridine 1-oxide was added to 78.5 g (1 mol) of acetyl chloride at -10°C. The obtained mixture was stirred under cooling with ice for 0.5 hour. After the completion of the reaction, 300 ml of ice-water was added to the reaction mixture. The obtained mixture was neutralized with sodium carbonate and extracted with chloroform. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated under a reduced pressure and purified by silica gel column chromatography (ethyl acetate/n-hexane/methanol) to obtain 4.7 g of the title compound.

^{1}H-NMR($CDCl_3$) δ ; 2.48(s,3H), 6.94~7.30(m, 2H), 8.09(d,J=7.2Hz,1H)

Preparative Example 24

4-(3-Methoxypropoxy)-2,3,5-trimethylpyridine 1-oxide



4.5 g (0.05 mol) of methoxypropanol was dissolved in 45 ml of dimethyl sulfoxide to obtain a solution. 2.0 g of 60% sodium hydride was added to this solution at a room temperature in a nitrogen atmosphere. The obtained mixture was heated to 60°C and stirred for one hour. After the completion of the reaction, a solution of 4.3 g (0.025 mol) of 4-chloro-2,3,5-trimethylpyridine 1-oxide in 15 ml of dimethyl sulfoxide was dropwise added to the reaction mixture at a room temperature. The obtained mixture was stirred at 60°C for 5 hours, cooled and distilled to dryness to remove the solvent. 200 ml of water was added to the obtained residue. The obtained mixture was extracted with 150 ml of chloroform five times. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled to remove the solvent. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane) to obtain 4.27 g of the title compound as an oil.

Preparative Example 25

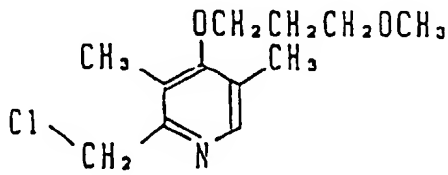
2-Hydroxymethyl-4-(3-methoxypropoxy)-3,4-dimethylpyridine

4.25 g (0.019 mol) of 4-(3-methoxypropoxy)-2,3,5-trimethylpyridine 1-oxide was dissolved in 40 ml of acetic anhydride to obtain a solution. This solution was stirred at 100°C for 30 minutes, cooled and distilled to remove the solvent. Thus, an oil was obtained. 50 ml of 1N hydrochloric acid was added to the oil. The obtained mixture was stirred at 100°C for one hour, cooled, neutralized with sodium hydrogencarbonate and extracted with 150 ml of chloroform thrice. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled to remove the solvent. The obtained residue was dried in a vacuum to obtain 4.70 g of the title compound as a crude oil.

^{1}H-NMR($CDCl_3$) δ ; 1.80~2.28(m,2H), 2.08(s, 3H), 2.23(s,3H), 3.34(s,3H), 3.58(t,J= 6.2Hz,2H), 3.87(t,J = 6.2Hz, 2H), 4.57(s, 2H), 8.10(s,1H)

Preparative Example 26

2-Chloromethyl-4-(3-methoxypropoxy)-3,5-dimethylpyridine

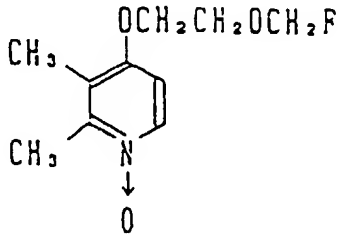


4.70 g of crude 2-hydroxymethyl-4-(3-methoxypropoxy)-3,5-dimethylpyridine was dissolved in 50 ml of chloroform to obtain a solution. A solution of 2.7 g of thionyl chloride in 10 ml of chloroform was dropwise added to the above solution at 0°C and the obtained mixture was stirred at 0°C for one hour. After the completion of the reaction, the reaction mixture was neutralized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with 150 ml of chloroform twice. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled to remove the solvent. The obtained residue was dried in a vacuum to obtain 4.52 g of the title compound as a crude oil.

^{1}H-NMR($CDCl_3$) δ ; 1.70~2.20(m,2H), 2.26(s, 3H), 2.34(s,3H), 3.38(s,3H), 3.61(t,J= 6.2Hz,2H), 3.91(t,J = 6.2Hz, 2H), 4.67(s, 2H), 8.18(s,1H)

Preparative Example 27

4-(2-Fluoromethoxy)ethoxy-2,3-dimethylpyridine N-oxide

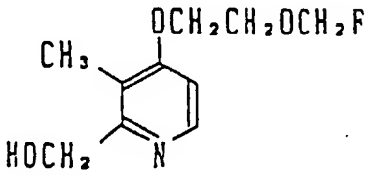


0.49 g of sodium hydride was gradually added to a solution of 1.0 g of 4-(2-hydroxyethoxy)-2,3-dimethylpyridine N-oxide in 40 ml of dimethylformamide in a nitrogen atmosphere at a room temperature. After the stopping of foaming, 1 ml of bromofluoromethane was added to the obtained mixture at -50°C. The resulting mixture was gradually heated and stirred at 15 to 20°C for 3 hours. Ethanol was added to the resulting mixture to consume excess sodium hydride. 5 ml of 1N aqueous hydrochloric acid was added to the mixture and gaseous nitrogen was passed through the obtained mixture to expel excess bromofluoromethane. Water was added to the resulting mixture. The obtained mixture was extracted with chloroform and the extract was dried over magnesium sulfate and distilled under a reduced pressure to remove the solvent. The residue was chromatographed over a silica gel column and eluted with chloroform containing 1 to 5% of methanol to obtain 0.6 g of the title compound.

^{1}H-NMR($CDCl_3$) δ ; 2.24(s,3H), 2.56(s,3H), 4.24(m,5H), 5.3(d,J = 55.8Hz,2H), 6.54 (d,J =6.2Hz,1H), 8.12(d,J = 6.2Hz,1H)

Preparative Example 28

4-(2-Fluoromethoxy)ethoxy-2-hydroxymethyl-3-methylpyridine



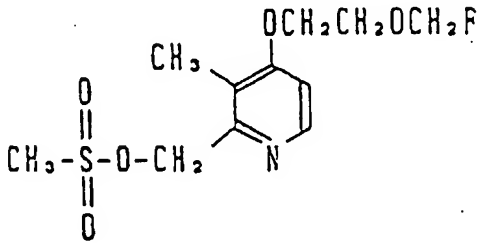
A mixture comprising crude 4-(2-fluoromethoxy)ethoxy-2,3-dimethylpyridine N-oxide prepared from 6.0 g of crude 4-(2-hydroxyethoxy)-2,3-dimethylpyridine N-oxide and 40 ml of acetic anhydride was stirred under heating at 90 to 100°C for 40 minutes and distilled under a reduced pressure to remove the acetic anhydride. The residue was made weakly basic with a 2N aqueous solution of sodium carbonate and extracted with chloroform. The extract was dried over magnesium sulfate and distilled under a reduced pressure to remove the solvent. The obtained residue was dissolved in 30 ml of ethanol, followed by the addition of 0.38 g of sodium hydroxide. The obtained mixture was stirred at a room temperature for 30 minutes, made weakly basic with a saturated aqueous solution of ammonium chloride and extracted with chloroform. The extract was dried over magnesium sulfate and distilled under a reduced pressure to remove the solvent. The residue was chromatographed over a silica gel column and eluted with ethyl acetate/n-

hexane to obtain 1.2 g of the title compound as a crystal.

^{1}H-NMR($CDCl_3$) δ ; 2.06(s,3H), 4.17(m,4H), 4.64(s,2H), 5.35(d,J = 56.3Hz,2H), 6.71 (d,J = 5.7Hz,1H), 8.30(d,J = 5.7Hz,1H)

Preparative Example 29

{4-(2-Fluoromethoxy)ethoxy-3-methylpyridine-2-yl}-methyl methanesulfonate

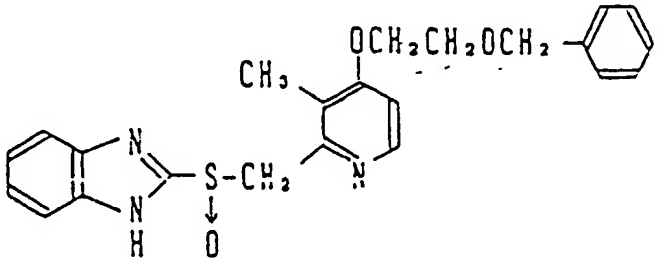


160 mg of methanesulfonyl chloride was dropwise added to a solution of 0.2 g of 4-(2-fluoromethoxy)-ethoxy-2-hydroxymethyl-3-methylpyridine and 143 mg of triethylamine in 10 ml of chloroform under dehumidifying at -50°C. The obtained mixture was gradually heated to a room temperature, made basic with a saturated aqueous solution of sodium hydrogencarbonate and extracted with chloroform. The extract was dried over magnesium sulfate and distilled to remove the solvent. 0.38 g of the title compound was obtained as a crude oil.

^{1}H-NMR($CDCl_3$) δ ; 2.30(s,3H), 3.08(s,3H), 4.2(m,4H), 5.4(d,J=55.8Hz,2H), 5.38(s,2H), 6.84(d,J = 6Hz,1H), 8.36 (d,J = 6Hz,1H)

Example 1

2-[{4-(2-Benzyloxyethoxy)-3-methylpyridine-2-yl)methylsulfinyl]benzimidazole



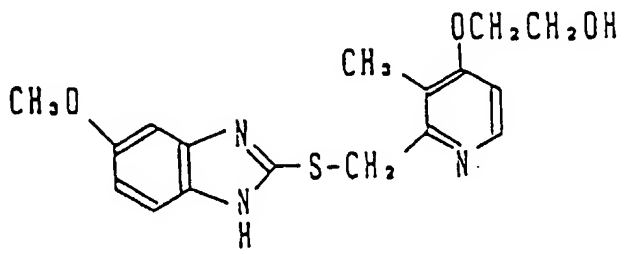
0.98 g of the thio ether prepared above was dissolved in 40 ml of dichloromethane to obtain a solution. 521 mg of m-chloroperbenzoic acid was added to the solution in portions at a temperature of -30 to -40°C, followed by the addition of 461 mg of triethylamine. The obtained mixture was heated to 0°C, followed by the addition of 20 ml of a 1N aqueous solution of sodium carbonate. The obtained mixture was stirred for 30 minutes and extracted with dichloromethane. The extract was washed with a saturated aqueous solution of common salt, dried over magnesium sulfate and distilled to remove the dichloromethane. The obtained residue was crystallized from a dichloromethane/ether mixture to obtain 0.78 g of the title compound as a crystal.

M^{+1} (determined according to FAB mass spectrometry: the same applies hereinafter): 422

^{1}H-NMR($CDCl_3$) δ ; 2.2(s,3H), 3.65~3.98(m, 2H), 4.04~4.28(m,2H), 4.59(s,2H), 4.78(s,2H), 6.98(d,J =4.6Hz, 1H), 7.05~7.8(m,9H), 8.22(d,J =4.6Hz,1H), 13.6(bs, 1H)

Example 2

2-[4-(2-Hydroxyethoxy)-3-methylpyridine-2-yl]methylthio-5-methoxy-1H-benzimidazole

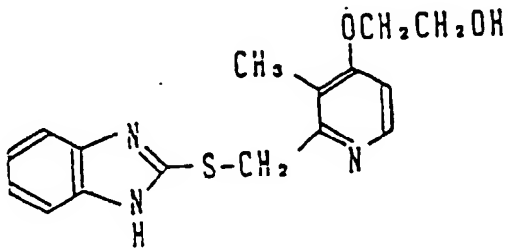


60 ml of ethanol was added to a mixture comprising 0.7 g of 2-chloromethyl-4-(2-hydroxyethoxy)-3-methylpyridine, 0.63 g of 2-mercapto-5-methoxy-1H-benzimidazole and 0.16 g of sodium hydroxide to obtain a mixture. This mixture was stirred at 60°C for one hour, concentrated and purified by silica gel column chromatography to obtain 1.08 g of the title compound.

^{1}H-NMR(DMSO-d_6) δ ;
2.2(s,3H), 3.72(s,3H), 3.6~4.1(m,4H), 4.6(s,2H), 6.6~7.35(m,4H), 8.14(d,J = 6Hz, 1H)

Example 3

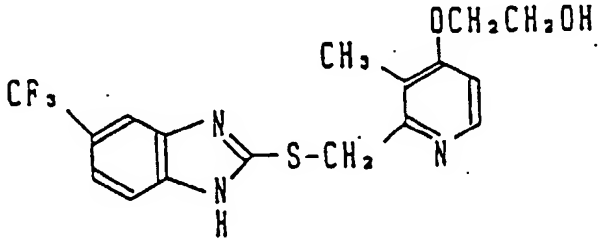
2-[4-(2-Hydroxyethoxy)-3-methylpyridine-2-yl]methylthio-1H-benzimidazole



The title compound was prepared in a similar manner to that described in Example 2. ^{1}H-NMR(DMSO-d_6) δ ;
2.24(s,3H), 3.6~4.18(m,4H), 4.7(s,2H), 6.93(d,J = 6Hz,1H), 7.0~7.6(m,4H), 8.25 (d,J = 6Hz,1H)

Example 4

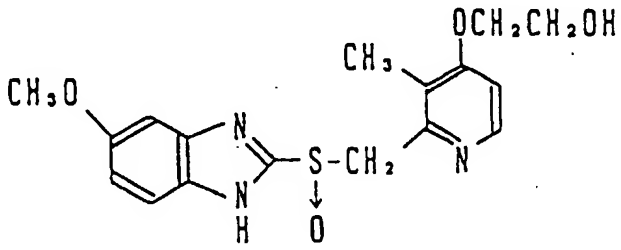
2-[4-(2-Hydroxyethoxy)-3-methylpyridine-2-yl]methylthio-5-trifluoromethyl-1H-benzimidazole



The title compound was prepared in a similar manner to that described in Example 2. ^{1}H-NMR(DMSO-d_6) δ ;
2.25(s,3H), 3.6~4.2(m,4H), 4.75(s,2H), 6.96(d,J = 6Hz,1H), 7.3 ~7.9(m,3H), 8.25 (d,J =6Hz,1H)

Example 5

2-[4-(2-Hydroxyethoxy)-3-methylpyridine-2-yl]methylsulfinyl-5-methoxy-1H-benzimidazole



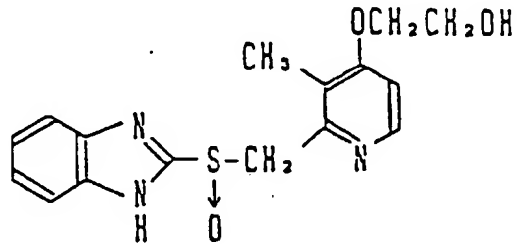
0.9 g of 2-[4-(2-hydroxyethoxy)-3-methylpyridine-2-yl]methylthio-5.methoxy-1H-benzimidazole was dissolved in a mixture comprising 5 ml of methanol and 80 ml of dichloromethane to obtain a solution. 0.51 g of m-chloroperbenzoic acid was added to this solution at -60°C. The obtained mixture was stirred at -50 to -40°C for 4.5 hours, followed by the addition of 0.38 g of triethylamine. A saturated aqueous solution of sodium hydrogencarbonate was added to the obtained mixture and the resulting mixture was extracted with chloroform. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled under a reduced pressure to obtain a crude product. This crude product was crystallized from dichloromethane/isopropyl ether to obtain 0.58 g of the title compound.

^{1}H-NMR(DMSO-d_6) δ ;

2.17(s,3H), 3.8(s,3H), 3.6~4.18(m,4H), 4.73(ABq,J = 14Hz,Δν = 8Hz,2H), 6.8 ~7.6(m,4H),8.21(d,J = 6Hz,1H)

Example 6

2-[4-(2-Hydroxyethoxy)-3-methylpyridine-2-yl]methylsulfinyl-1H-benzimidazole



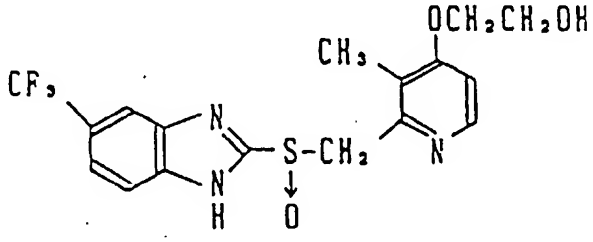
The title compound was prepared in a similar manner to that described in Example 5. M^{+1} :332

^{1}H-NMR(DMSO-d_6) δ ;

2.17(s,3H), 3.6~4.2(m,4H), 4.74(s,2H), 6.95(d,J = 6Hz,1H), 7.18~7.77(m,4H), 8.22 (d,J = 6Hz,2H)

Example 7

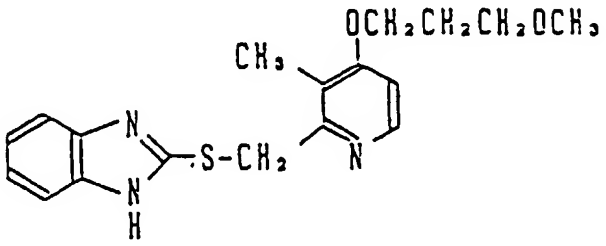
2-[4-(2-Hydroxyethoxy)-3-methylpyridine-2-yl]methylsulfinyl-5-trifluoromethyl-1H-benzimidazole



The title compound was prepared in a similar manner to that described in Example 5.

Example 8

2-[{4-(3-Methoxypropoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole



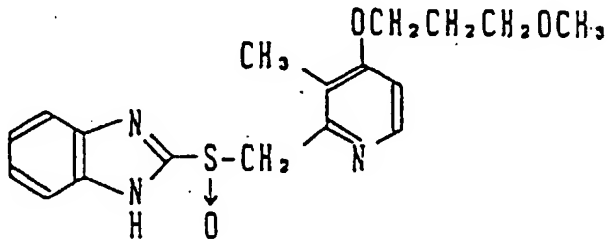
20 cc of ethanol was added to a mixture comprising 280 mg (1.8 mmol) of 2-mercapto-1H-benzimidazole, 470 mg (2 mmol) of 2-chloromethyl-4-(3-methoxypropoxy)-3-methylpyridine and 100 mg (2.4 mmol) of sodium hydroxide. The obtained mixture was stirred at 50°C for 3 hours. After the completion of the reaction, the reaction mixture was distilled to remove the ethanol. The obtained residue was purified by silica gel column chromatography to obtain 590 mg of 2-[{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylthio]-1 H-benzimidazole as a pale yellow crystal.

^{1}H-NMR($CDCl_3$) δ ;

2.09(t,J=6.1Hz,2H), 2.26(s,3H), 3.35(s,3H), 3.56(t,J=6.1Hz,2H), 4.13(t,J=6.1Hz,2H), 4.37(s,2H), 6.76(d,J = 6.1 Hz, 1H), 7.1~7.25 (m,2H), 7.5(br,s,2H), 8.33(d,J = 6.1 Hz,1H)

Example 9

2-{4-(3-Methoxypropoxy)-3-methylpyridine-2-yl}methylsulfinyl-1H-benzimidazole



5 g of 2-[{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylthio]-1H benzimidazole was dissolved in a mixture comprising 100 ml of dichloromethane and 25 ml of diethyl ether to obtain a solution. 2.83 g of 85% m-chloroperbenzoic acid was added to this solution in portions at -45°C. After the completion of the reaction, 2 g of triethylamine was added to the reaction mixture and the obtained mixture was heated to -10°C, followed by the addition of 50 ml of 1N sodium hydroxide. The obtained mixture was stirred at room temperature for 30 minutes. The obtained aqueous layer was washed with 20 ml of dichloromethane twice and adjusted to pH 11 with a 2 M aqueous solution of ammonium acetate. The aqueous layer was extracted with 50 ml of dichloromethane thrice. The obtained dichloromethane layer was washed with 50 ml of a saturated aqueous solution of sodium hydrogencarbonate twice, dried over magnesium sulfate and distilled to remove the dichloromethane. The obtained oily product was crystallized from dichloromethane/ether to obtain 4.17 g of the title compound as a white crystal.

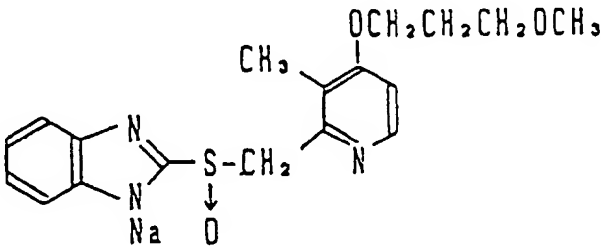
M.p.: 99 to 100°C (dec.).

^{1}H-NMR($CDCl_3$) δ ;

1.83~2.09(m,2H), 2.13(s,3H), 3.34(s,3H), 3.52(t,J=6.2Hz,2H), 4.05(t,J=6.2Hz,2H), 4.79(s,2H), 6.70(d,J =5.7Hz,1H), 7.07~7.30(m,2H), 7.30~7.60(br,s,2H), 8.27(d, J =5.7Hz,1H)

Example 10

Sodium salt of 2-[{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylsulfinyl]-1H-benzimidazole



500 mg (1.46 mmol) of 2-[{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole was dissolved in 20 cc of dichloromethane to obtain a solution. 320 mg of 85% m-chloroperbenzoic acid was added to this solution in portions at -45°C. After the completion of the reaction, 370 mg of triethylamine was added to the reaction mixture. The obtained mixture was heated to -10°C, followed by the addition of 30 ml of a saturated aqueous solution of sodium carbonate. The obtained mixture was stirred at a room temperature for 30 minutes and extracted with dichloromethane. The extract was dried over magnesium sulfate and distilled to remove the dichloromethane. Thus, a crude product was obtained. This crude product was dissolved in 14.6 cc of a 0.1 N aqueous solution of sodium hydroxide to obtain a solution. This solution was distilled together with 30 cc of ethanol thrice to remove the water as an azeotropic mixture with ethanol and dried in a vacuum. Ether was added to the obtained residue to precipitate a white crystal. This crystal was washed with ether thrice by decantation and dried in a vacuum to obtain 530 mg of sodium salt of 2-[{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylsulfinyl]-1H-benzimidazole.

M.p.: 140 to 141°C (dec.).

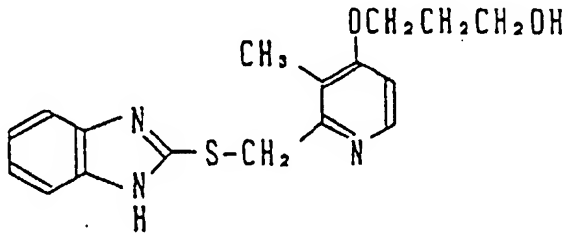
M^{+1} :382

^{1}H-NMR(DMSO-d_6) δ ;

1.99(t,J = 6.1 Hz,2H), 2.17(s,3H), 3.25(s,3H), 3.49(t,J = 6.1 Hz,2H), 4.09(t,J = 6.1 Hz,2H), 4.56(ABq,J =14.1Hz,Δν = 21.3Hz,2H), 6.8~6.9(m,3H), 7.4~7.5(m,2H), 8.27(d,J = 5.7Hz, 1H)

Example 11

2-[{4-(3-Hydroxypropoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole



80 ml of ethanol was added to a mixture comprising 1.39 g (9.27 mmol) of 2-mercaptobenzimidazole, 2.0 g (9.27 mmol) of 2-chloromethyl-4-(3-hydroxypropoxy)-3-methylpyridineand 0.44 g (11.1 mmol) of sodium hydroxide. The obtained mixture was stirred at 50°C for one hour. After the completion of the reaction, the reaction mixture was concentrated. The obtained residue was purified by silica gel column chromatography to obtain 1.7 g of the title compound (56%).

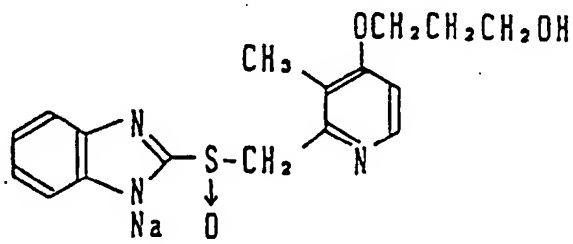
M^{+1}:368

^{1}H-NMR(DMSO-d_6) δ ;

1.8~2.1(m,2H), 2.24(s,3H), 3.6(t,J =6Hz, 2H), 4.2(t,J =6Hz,2H), 4.7(s,2H), 7.0~7.38 (m,3H), 7.38~7.6(m,2H), 8.35 (d,J =6Hz,1H)

Example 12

Sodium salt of 2-[{4-(3-hydroxypropoxy)-3-methylpyridine-2-yl}methylsulfinyl]-1 H-benzimidazole

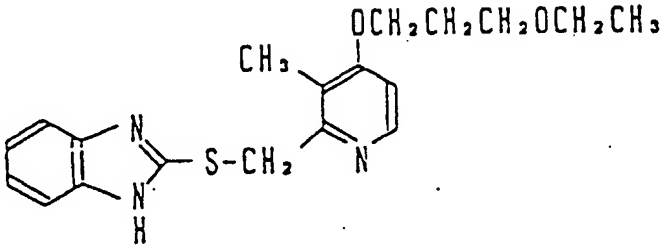


1.0 g (3.04 mmol) of 2-[{4-(3-hydroxypropoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole was dissolved in 100 ml of dichloromethane to obtain a solution. 580 mg of 90% m-chloroperbenzoic acid was added to this solution at -45°C. The obtained mixture was stirred for 2 hours. After the completion of the reaction, 470 mg of triethylamine was added to the reaction mixture. The obtained mixture was heated to -20°C, followed by the addition of 30 ml of a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was stirred at a room temperature for 30 minutes and extracted with chloroform. The obtained chloroform layer was concentrated to obtain a crude product. This crude product was crystallized from dichloromethane/ether to obtain 830 mg of 2-[{4-(3-hydroxypropoxy)-3-methylpyridine-2-yl}methylsufinyl]-1 H-benzimidazole. This product was dissolved in 24 ml of 0.1 N aqueous sodium hydroxide. The obtained solution was distilled together with ethanol to remove the water as an azeotropic mixture with ethanol and dried under vacuumizing with a vacuum pump. Ether was added to the obtained residue to precipitate a colorless crystal. This crystal was separated by filtration. Thus, 860 mg of the title compound was obtained (77%).

^{1}H-NMR(DMSO-d_6) δ ;
1.7 -2.1(m,2H), 2.16(s,3H), 3.58(t,J=6Hz, 2H), 4.12(t,J=6Hz,2H), 4.55(ABq,J=13Hz, Δν = 20Hz,2H), 6.7-7.0(m,3H), 7.3-7.6(m,2H), 8.27(d,J = 6Hz,1H)

Example 13

2-[{4-(3-Ethoxy)propoxy-3-methylpyridine-2-yl)methylthio]-1H-benzimidazole

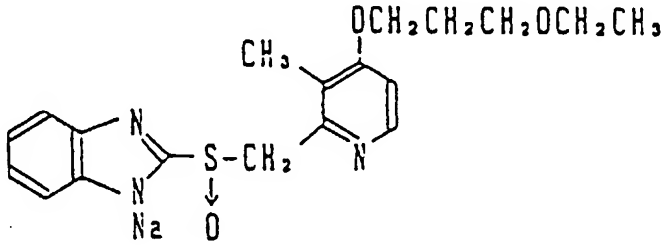


A mixture comprising 4.2 g of {4-(3-ethoxypropoxy)-3-methylpyridine-2-yl}methyl methanesulfonate, 1.87 g of 2-mercaptobenzimidazole and 30 ml of ethanol was stirred at a room temperature for one hour and distilled to remove the ethanol. The obtained residue was purified by silica gel column chromatography to obtain 0.88 g of the title compound and 5.1 g of methanesulfonate of the title compound.

^{1}H-NMR($CDCl_3$) δ ; 1.19(t,J=7.0Hz,3H), 1.9 -2.1(m,2H), 2.24(s,3H), 3.48(q,J=7.0 Hz,2H), 3.58-(t,J = 6.2Hz,2H), 4.11(t,J =6.2Hz,2H), 4.38(s,2H), 6.73(d,J =5.7Hz, 1H), 6.97 -7.20(m,2H), 7.32-7.55(m,2H), 8.31(d,J = 5.7Hz,1H)

Example 14

Sodium salt of 2-[{4-(3-ethoxypropoxy)-3-methylpyridine-2-yl}methylsulfinyl]-1H-benzimidazole

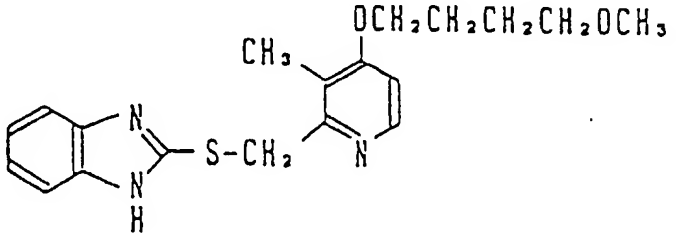


0.6 g of 2-[{4-(3-ethoxypropoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole was dissolved in 30 ml of dichloromethane to obtain a solution. 0.37 g of 85% m-chloroperbenzoic acid was added to this solution at -45°C. After 2 hours, 0.43 g of triethylamine was added to the obtained mixture, followed by the addition of 30 ml of a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was vigorously stirred at a room temperature for one hour and extracted with dichloromethane. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated to obtain a residue. This residue was dissolved in 16 ml of 0.1N aqueous sodium hydroxide and the obtained solution was distilled to remove the water. The residue was dried under a reduced pressure and crystallized from ether to obtain 0.54 g of the title compound.

^{1}H-NMR(DMSO-d_6) δ ; 1.11(t,J =7.0Hz,3H), 1.7 ~2.1(m,2H), 2.15(s,3H), 3.2~3.6(m,4H), 3.65(s,3H), 4.09(t,J = 6.2Hz,2H), 4.49 (ABq,J = 11.8Hz,Δν = 17.0Hz,2H), 6.65~ 7.0(m,3H), 7.2~7.6(m,2H), 8.2(d,J = 5.6 Hz,1H)

Example 15

2-[{4-(4-Methoxybutoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole

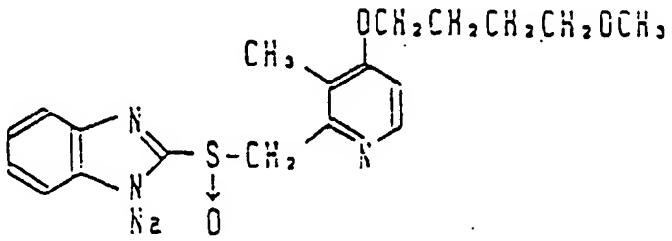


611 mg of triethylamine and 686 mg of methanesulfonyl chloride were added to a solution of 0.84 g of crude 2-hydroxy-4-(4-methoxybutoxy)-3-methylpyridine in 30 ml of dichloromethane at -20°C under stirring and dehumidifying to obtain a mixture. This mixture was gradually brought to room temperature, followed by the addition of a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was stirred for 30 minutes and extracted with chloroform. The extract was dried over magnesium sulfate and distilled under a reduced pressure to remove the chloroform. Thus, a red oil was obtained. 560 mg of 2-mercapto-1H-benzimidazole and 30 ml of ethanol were added to this oil. The obtained mixture was stirred at a room temperature for 30 minutes, made basic with a 2N aqueous solution of sodium carbonate and extracted with chloroform. The extract was dried over magnesium sulfate and distilled under a reduced pressure to remove the chloroform. The obtained residue was chromatographed over a silica gel column and eluted with ethyl acetate/n-hexane to obtain 0.42 g of an oil.

^{1}H-NMR($CDCl_3$) δ ; 1.4~2.16(m,4H), 2.26(s,3H), 3.35(s,3H), 3.45(t,J =5.72Hz,2H), 4.06(t,J = 5.72Hz,2H), 4.37 (s,2H), 6.74 (d,J = 5.71Hz,1H), 7.1~7.25(m,2H), 7.48~7.56(m,2H), 8.33(d,J = 5.72Hz,1 H)

Example 16

Sodium salt of 2-[{4-(4-methoxybutoxy)-3-methylpyridine-2-yl}methylsulfinyl]-1H-benzimidazole



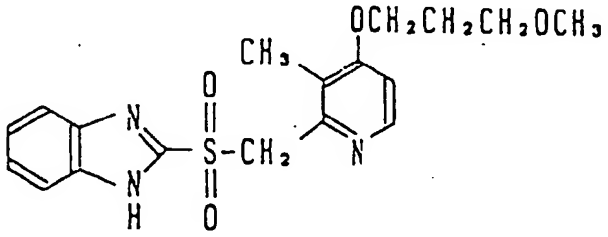
0.4 g of 2-[{4-(4-methoxybutoxy)-3-methylpyridine-2-yl)methylthio]-1H-benzimidazole was dissolved in 40 ml of dichloromethane under dehumidifying to obtain a solution. 227 mg of m-chloroperbenzoic acid was added in portions to this solution at -40°C. The obtained mixture was stirred for 30 minutes, followed by the addition of 160 mg of triethylamine. The obtained mixture was heated to -20°C, followed by the addition of 30 ml of a 2N aqueous solution of sodium carbonate. The obtained mixture was stirred for 40 minutes and extracted with dichloromethane. The extract was washed with a saturated aqueous solution of sodium hydrogencarbonate, dried over magnesium sulfate and distilled under a reduced pressure to remove the dichloromethane. Thus, 0.43 g of an oily product was obtained. This product was dissolved in a mixture comprising 11.2 ml of 0.1N aqueous sodium hydroxide and 30 ml of ethanol and the obtained solution was distilled under a reduced pressure to remove the solvent. Ethanol was added to the obtained residue and the obtained mixture was distilled under a reduced pressure to remove the solvent. The residue was crystallized from ethanol/ether to obtain 0.37 g of the title compound as a crystal.

^{1}H-NMR(DMSO-d_6) δ ; 1.84(m,4H), 2.16(s,3H), 3.24(s,3H), 3.38(t,J=6.2Hz,2H), 4.06(t,J=6.2Hz,2H), 4.55(ABq, J = 13.2Hz,Δν = 18.1 Hz,2H), 6.8~6.98(m,3H), 7.4~7.6(m,2H), 8.27(d,J = 5.3Hz,1H)

The following compounds were prepared in a similar manner to those described above.

Example 17

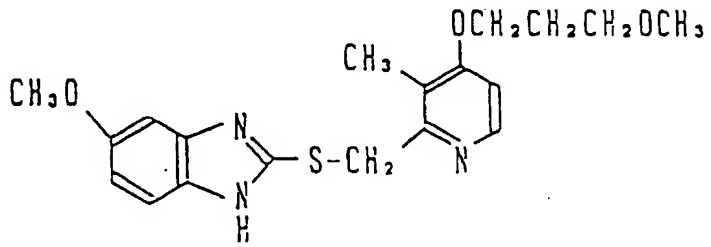
2-[{4-(2-Methoxy)propoxy-3-methylpyridine-2-yl}methylsulfonyl]-1H-benzimidazole



^{1}H-NMR(DMSO-d_6) δ ; 2.0(t,J =7.5Hz,2H), 2.2 (s,3H), 3.28(s,3H), 3.5(t,J =7.5Hz,2H), 4.09(t,J = 7.5Hz,2H), 5.06 (s,2H), 6.92(d,J = 5.4Hz,1H), 7.35 ~7.52(m,2H), 7.64~7.8(m,2H), 8.03(d,J = 5.4Hz,1H)

Example 18

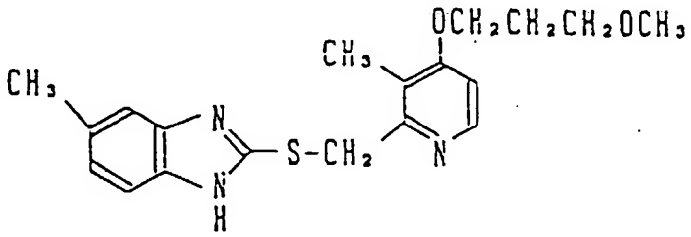
5-Methoxy-2-{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylthio-1H-benzimidazole



^{1}H-NMR($CDCl_3$ δ ;
1.92~2.18(m,2H), 2.22(s,3H), 3.31(s,3H), 3.52(t,J=6.1Hz,2H), 3.80(s,3H), 4.09(t,J=6.1Hz,2H), 4.30(s,2H), 6.64~6.81 (m,2H), 6.97(d,J = 2.2Hz,1H), 7.33(d,J = 8.5Hz), 8.25 (d,J = 5.7Hz,1H)

Example 19

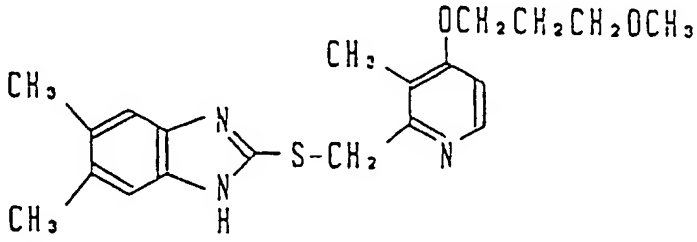
5-Methyl-2-{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylthio-1H-benzimidazole



^{1}H-NMR($CDCl_3$) δ ;
1.94-2.19(m,2H), 2.22(s,3H), 2.42(s,3H), 3.31(s,3H), 3.52(t,J=6.1Hz,2H), 4.08(t,J=6.1Hz,2H), 4.31(s,2H), 6.67(d,J = 5.7Hz, 1H), 6.80 ~7.00(m,1H), 7.15~7.40(m,2H), 8.23(d,J = 5.7Hz,1 H)

Example 20

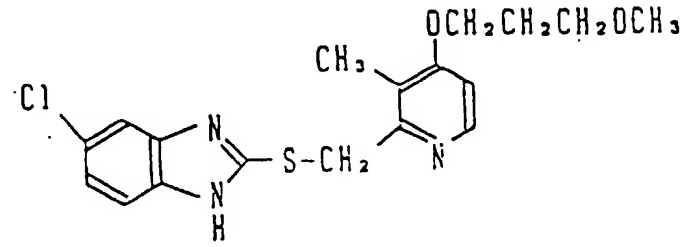
5,6-Dimethyl-2-{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylthio-1H-benzimidazole



^{1}H-NMR($CDCl_3$) δ ;
1.95~2.17(m,2H), 2.24(s,3H), 2.34(s,6H), 3.35(s,3H), 3.55(t,J=6.2Hz,2H), 4.12(t,J=6.2Hz,2H), 4.35(s,2H), 6.74(d,J = 5.7Hz), 7.29(s,2H), 8.32(d,J = 5.7Hz)

Example 21

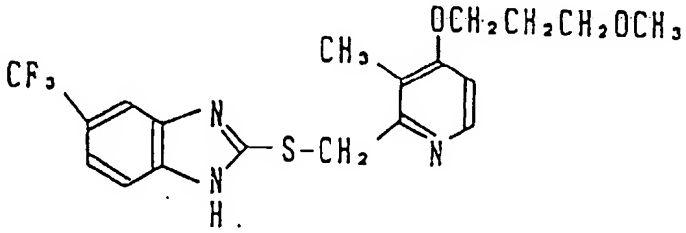
5-Chloro-2-{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylthio-1H-benzimidazole



^{1}H-NMR($CDCl_3$) δ ;
1.93~2.18(m,2H), 2.25(s,3H), 3.35(s,3H), 3.56(t,J=6.2Hz,2H), 4.13(t,J=6.2Hz,2H), 4.36(s,2H), 6.76(d,J = 5.7Hz,1H), 7.10(dd,J = 8.8Hz,2.2Hz,1H), 7.42(d,J = 8.8Hz,1H), 7.50(d,J = 2.2Hz,1H), 8.31(d,J = 5.7Hz,1H)

Example 22

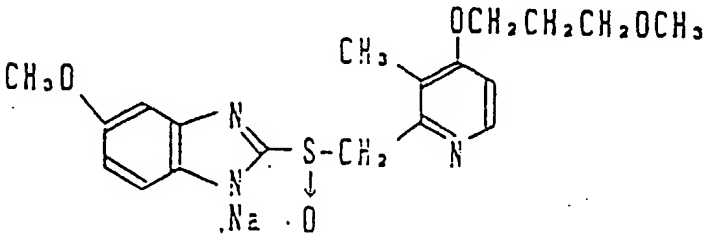
2-{4-(3-Methoxypropoxy)-3-methylpyridine-2-yl}methylthio-5-trifluoromethyl-1H-benzimidazole



^{1}H-NMR($CDCl_3$) δ;
1.92~2.19(m,2H), 2.27(s,3H), 3.36(s,3H), 3.56(t,J=5.9Hz,2H), 4.15(t,J=6.1Hz,2H), 4.38(s,2H), 6.79(d,J = 5.7Hz,1H), 7.23-7.60(m,2H), 7.71(s,1H), 8.35(d,J = 5.7Hz, 1H)

Example 23

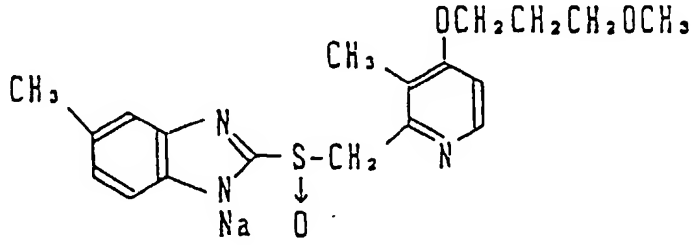
Sodium salt of 5-methoxy-2-{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylsulfinyl-1H-benzimidazole



^{1}H-NMR(DMSO-d_6) δ ;
1.84~2.06(m,2H), 2.14(s,3H), 3.25(s,3H), 3.49(t,J=6.2Hz,2H), 3.72(s,3H), 4.09(t,J=6.2Hz,2H), 4.53(ABq,J = 2.7Hz, Δν = 18.0Hz, 2H), 6.54(dd,J = 8.8Hz,2.6Hz,1H), 6.91 (d,J = 5.7Hz,1H), 7.00(d,J = 2.6Hz,1 H), 7.34(d,J = 8.8Hz,1H), 8.27(d,J = 5.7Hz,1H)

Example 24

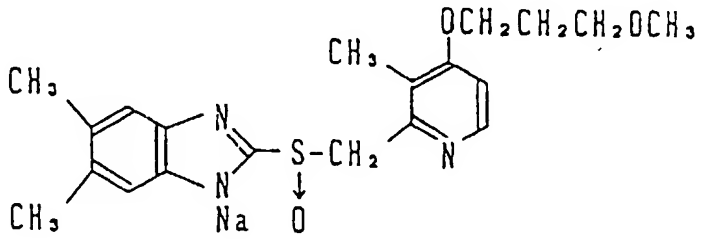
Sodium salt of 5-methyl-2-{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylsulfinyl-1H-benzimidazole



^{1}H-NMR(DMSO-d_6) δ ;
1.84~2.05(m,2H), 2.14(s,3H), 2.37(s,3H), 3.25(s,3H), 3.48(t,J=6.2Hz,2H), 4.09(t,J=6.2Hz,2H), 4.53(ABq,J = 12.8Hz, Δν = 17.3Hz,2H), 6.71 (dd,J = 7.9Hz,1.5Hz,1H), 6.91 (d,J = 5.7Hz,1 H), 7.26(s,1 H), 7.35(d,J = 7.9Hz,1H), 8.27(d,J = 5.7Hz,1H)

Example 25

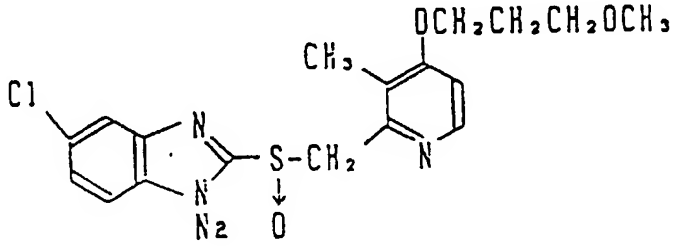
Sodium salt of 5,6-dimethyl-2-{4-(3-methoxyporpoxy)-3-methylpyridine-2-yl}methylsulfinyl-1H-benzimidazole



^{1}H-NMR(DMSO-d_6) δ ;
1.82~2.08(m,2H), 2.13(s,3H), 2.27(s,6H), 3.24(s,3H), 3.47(t,J=6.6Hz,2H), 4.08(t,J=6.7Hz,2H), 4.54(ABq,J = 13.0Hz, Δν = 19.8Hz,2H), 6.90(d,J = 5.7Hz,1H), 7.25(s,2H), 8.26(d,J = 5.7Hz,1H)

Example 26

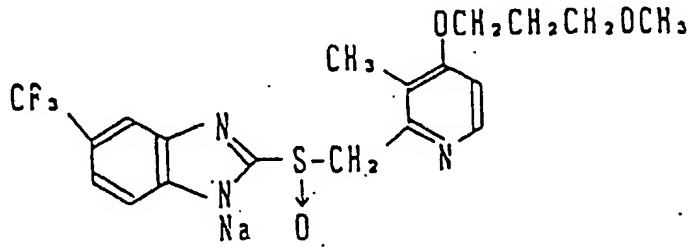
Sodium salt of 5-chloro-2-{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylsulfinyl-1H-benzimidazole



^{1}H-NMR(DMSO-d_6) δ ;
1 .80~2.06(m,2H), 2.13(s,3H), 3.25(s,3H), 3.48(t,J = 6.2Hz,2H), 4.09(t,J = 6.2Hz,2H), 4.54(ABq,J = 12.9Hz,Δν = 15.3Hz,2H), 6.65~6.92(m,2H), 7.25~7.50(m,2H), 8.27(d,J = 5.3Hz)

Example 27

Sodium salt of 2-{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylsulfinyl-5-trifluoromethyl-1H-benzimidazole

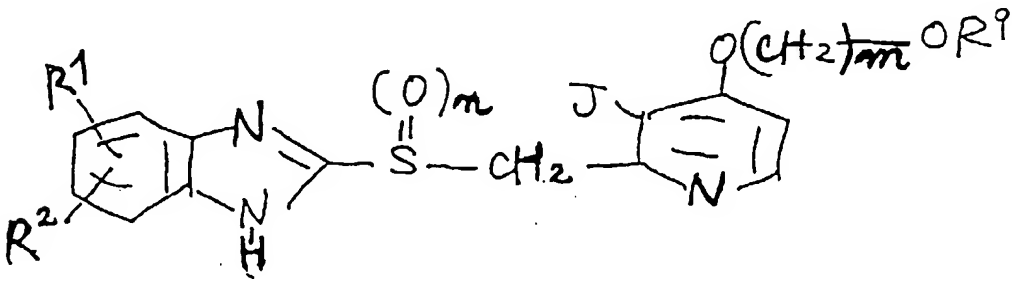


^{1}H-NMR(DMSO-d_6) δ ;
1.81~2.06(m,2H), 2.14(s,3H), 3.25(s,3H), 3.48(t,J = 6.2Hz,2H), 4.09(t,J = 6.1Hz,2H), 4.56(ABq,J = 13.2Hz,Δν = 13.5Hz,2H), 6.92(d,J = 5.3Hz,1 H), 7.01~7.22(m,1H), 7.45~7.82(m,2H), 8.21-(d,J = 5.3Hz,1H)

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A pyridine derivative represented by the general formula:



wherein R^1 and R^2 may be the same or different from each other and each stand for a hydrogen atom, a C_1-C_6 alkyl, C_1-C_6 alkoxy, halogenated C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl or carboxyl group or a halogen atom

J is a C_1-C_6 alkyl,
R^9 stands for a hydrogen atom or a C_1-C_6 alkyl group,
n stands for an integer of 0 to 2,
m stands for an integer of 2 to 10,

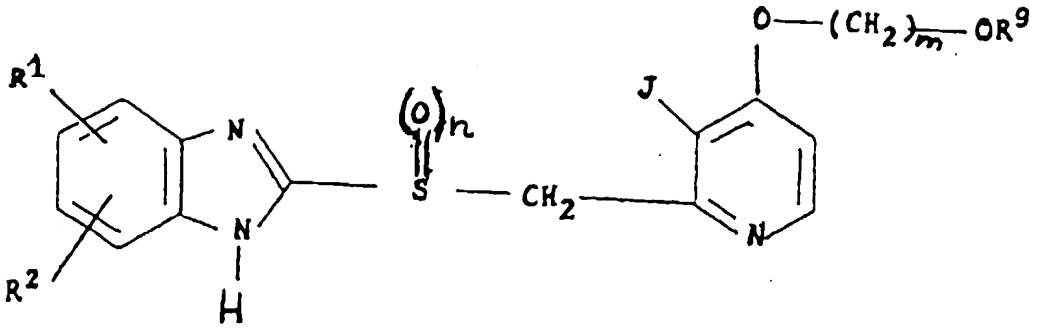
with the proviso that when R^9 is a C_1-C_6 alkyl group, m stands for an integer of 3 to 10, and a pharmaceutically acceptable salt thereof.

2. A pyridine derivative according to claim 1 wherein R^1 is hydrogen or C_1-C_6 alkyl and R^2 is hydrogen.

3. A pyridine derivative according to claim 1 or 2 wherein n is one, R^1 and R^2 are both hydrogen or R^1 is 5-C_1-C_6 alkyl, 5-halogenated C_1-C_6 alkyl or 5-C_1-C_6 alkoxy and R^2 is hydrogen, J is methyl and m is 3 to 10, and R^9 is C_1-C_6 alkyl.

4. A pyridine derivative according to claim 3, wherein R^1 and R^2 are both hydrogen, J is methyl, m is 3 and R^9 is methyl.

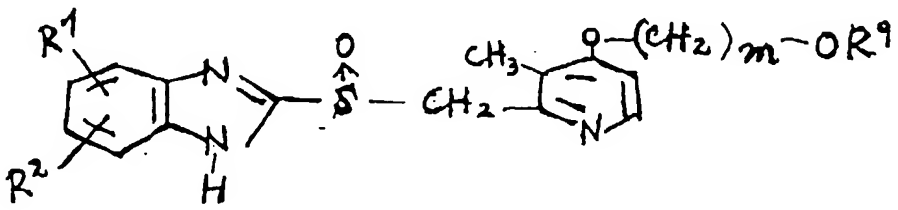
5. A pyridine derivative according to claim 1 represented by the formula



in which R^1 and R^2, which may be the same or different from each other are hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogented C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl or carboxyl group or a halogen atom;

n stands for an integer of 0 to 2,
J is a C_1-C_6 alkyl group,
m is an integer of 3 to 10, and
R^9 is a C_1-C_6 alkyl group; or a pharmaceutically acceptable salt thereof.

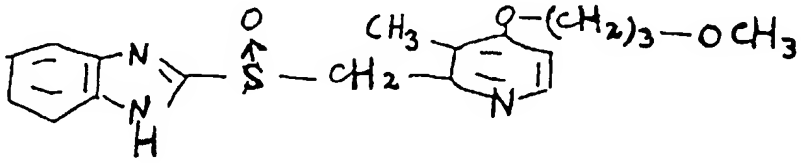
6. The pyridine derivative according to claim 1



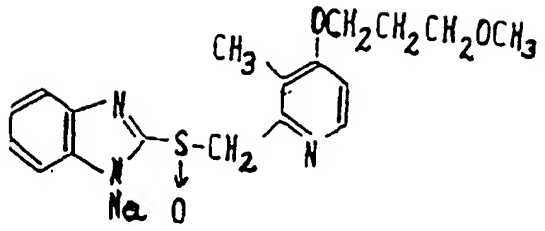
wherein R^1 and R^2, which may be the same or different from each other, are hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogenated C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl or carboxyl group or a halogen atom;

m is an integer of 3, and
R^9 is C_1-C_6 alkyl, or a pharmaceutically acceptable salt thereof.

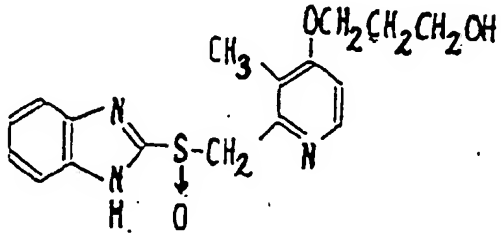
7. The pyridine derivative according to claim 1 represented by the formula



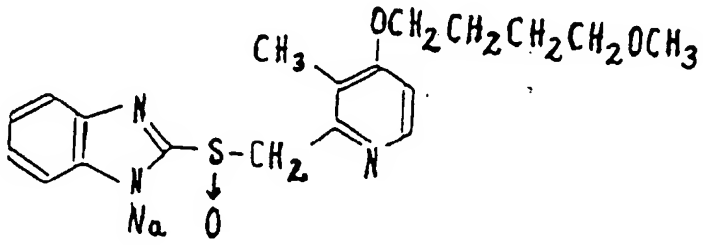
8. A pharmaceutically acceptable salt of the pyridine derivative according to claim 1 represented by the formula



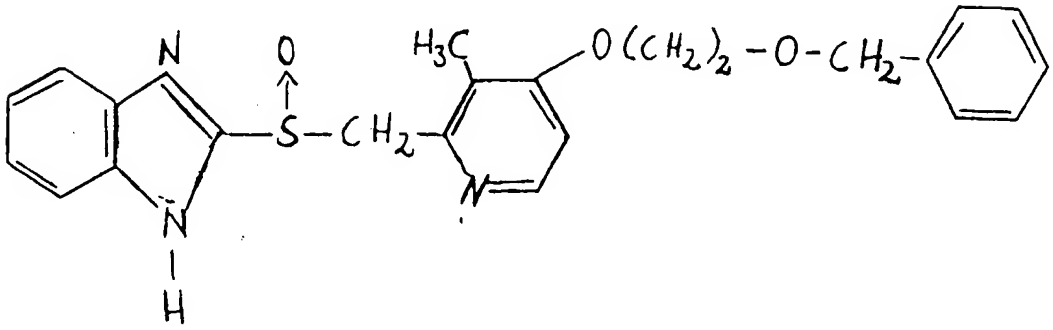
9. The pyridine derivative according to claim 1 represented by the formula



10. A pharmaceutically acceptable salt of the pyridine derivative according to claim 1 represented by the formula



11. A pyridine derivative of the structural formula



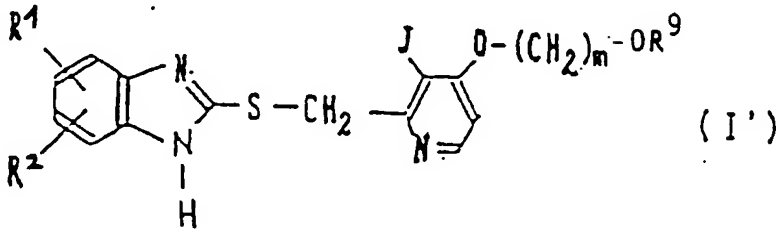
or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition which comprises a pharmacologically effective amount of a pyridine derivative according to any of claims 1-11 wherein n is 1, or a pharmacologically acceptable salt thereof and a pharmacologically acceptable carrier.

13. A pharmaceutical composition according to claim 12 which comprises 0,1 to 100 grams of the pyridine derivative or a pharmacologically acceptable salt thereof per unit dose.

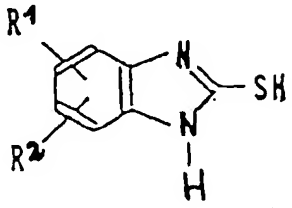
14. The use of a pyridine derivative according to any of claims 1-11 wherein n is 1, for the manufacture of a medicament for the treatment or the prevention of peptic ulcers.

15. A process for producing a compound of the general formula I'



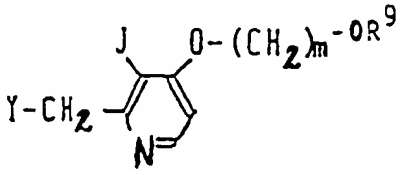
(I')

wherein R^1, R^2, m, R^9 and J are defined as in claim 1, or a pharmaceutically acceptable salt thereof comprising the steps of reacting the compound of formula II



(II)

wherein R^1 and R^2 are defined as above with the compound of the formula III



(III)

wherein J, m and R^9 are defined as above and Y represents a halogen atom or a sulfonyloxy group, and optionally converting the product into a salt.

16. A process according to claim 15 wherein Y represents chlorine, bromine or iodine.

17. A process according to claim 15 wherein Y represents an alkylsulfonyloxy group.

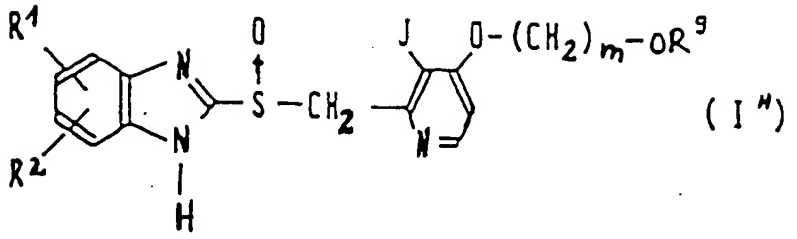
18. A process according to claim 17 wherein the alkylsulfonyloxy group is a methylsulfonyloxy group or an ethylsulfonyloxy group.

19. A process according to claim 15 wherein the sulfonyloxy group is an aromatic sulfonyloxy group.

20. A process according to claim 19 wherein the aromatic sulfonyloxy group is a benzenesulfonyloxy group or a tosyloxy group.

21. A process according to any of claims 15-20 wherein the reaction is carried out in the presence of an acid scavenger.

22. A process for producing a compound of formula I"

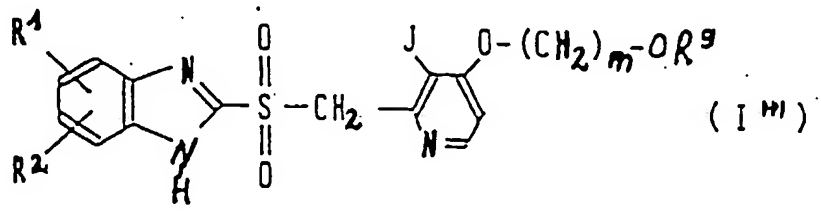


(I'')

wherein R^1, R^2, J, m and R^9 are defined as in claim 1, or a pharmaceutically acceptable salt thereof, comprising the steps of reacting the compound of formula I' as defined in claim 15 with an approximately equimolar amount of an oxidizing agent and optionally converting the product into a salt.

23. A process according to claim 22 wherein the oxidizing agent is selected from hydrogen peroxide, peracetic acid, m-chloroperbenzoic acid, sodium hypochlorite or sodium hypobromite.

24. A process for producing a compound of formula I'''

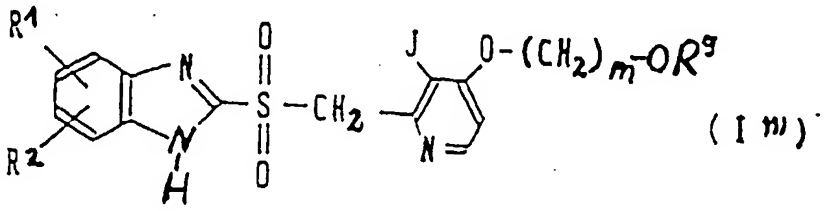


(I''')

wherein R^1, R^2, J, R^9 and m are as defined in claim 1, or a pharmaceutically acceptable salt thereof, comprising the step of reacting the compound of formula I' as defined in claim 15 with at least two molar equivalent amounts of an oxidizing agent, and optionally converting the product into a salt.

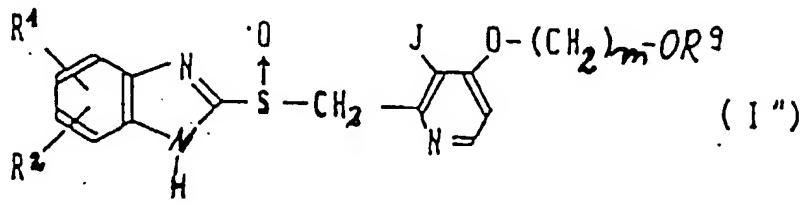
25. A process according to claim 24 wherein the oxidizing agent is selected from hydrogen peroxide, peracetic acid, m-chloroperbenzoic acid, sodium hypochlorite or sodium m-periodate.

26. A process for producing the compound of formula I'''



(I''')

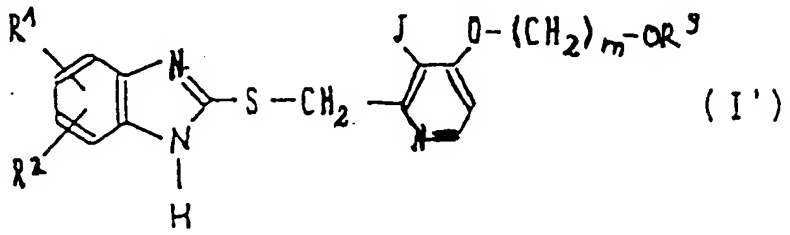
wherein R^1, R^2, , J, R^9 and m are as defined in claim 1, or a pharmaceutically acceptable salt thereof, comprising the step of reacting an oxidizing agent with the compound of formula I''



(I'')

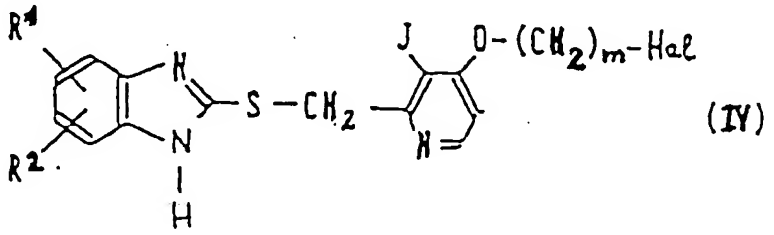
wherein R^1, R^2, , J, R^9 and m are as defined above, and optionally converting the product into a salt.

27. A process for producing a compound of the general formula I'



(I')

wherein R^1, R^2, J, m and R^9 are defined as in claim 1, or a pharmaceutically acceptable salt thereof comprising the steps of reacting a compound of the formula IV



(IV)

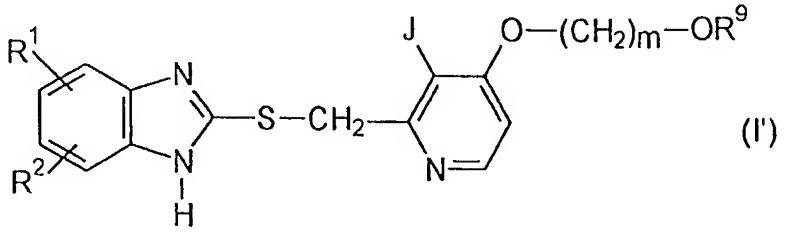
wherein R^1, R^2, J and m are defined as above and Hal represents a halogen atom, with a compound of formula R^9 OH, wherein R^9 is defined as above, and optionally converting the product into a salt.

28. A process according to claim 27 wherein the reaction is carried out in the presence of an acid scavenger.

29. The use of a pyridine derivative according to any of claims 1-11 wherein n is 1, for the manufacture of a medicament for the inhibition of gastric acid secretion.

Claims for the following Contracting States : ES, GR

1. A process for producing a compound of the general formula I'

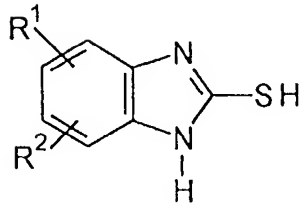


(I')

wherein R^1 and R^2 may be the same or different from each other and each stand for a hydrogen atom, a C_1-C_6 alkyl, C_1-C_6 alkoxy, halogenated C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl or carboxyl group or a halogen atom

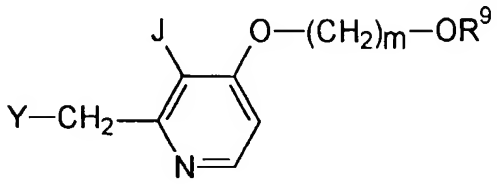
J is a C_1-C_6 alkyl,

R^9 stands for a hydrogen atom or a C_1-C_6 alkyl group, m stands for an integer of 2 to 10 with proviso that when R^9 is a C_1-C_6 alkyl group, m stands for an integer of 3 to 10, or a pharmaceutically acceptable salt thereof comprising the steps of reacting the compound of formula II



(II)

wherein R^1 and R^2 are defined as above with the compound of the formula III



(III)

wherein J, m and R^9 are defined as above and Y represents a halogen atom or a sulfonyloxy group, and optionally converting the product into a salt.

2. A process according to claim 1, wherein Y represents chlorine, bromine or iodine.

3. A process according to claim 1, wherein Y represents an alkylsulfonyloxy group.

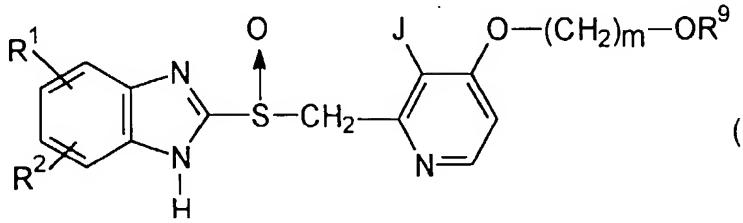
4. A process according to claim 3, wherein the alkylsulfonloxy group is a methylsulfonyloxy group or an ethylsulfonyloxy group.

5. A process according to claim 1, wherein the sulfonyloxy group in an aromatic sulfonyloxy group.

6. A process according to claim 5, wherein the aromatic sulfonyloxy group is a benzenesulfonyloxy group or a tosyloxy group.

7. A process according to claims 1-6 wherein the reaction is carried out in the presence of an acid scavenger.

8. A process for producing a compound of formula I"

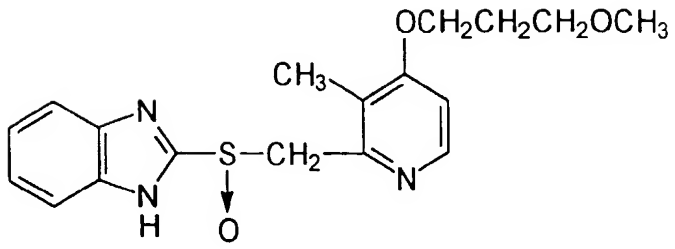


(I")

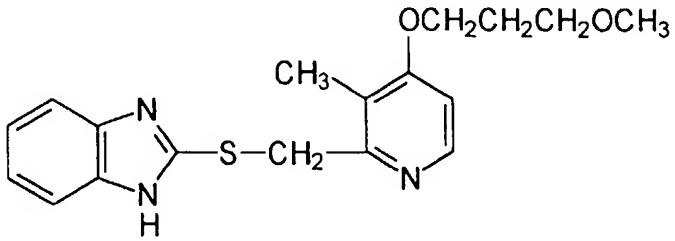
wherein R^1, R^2, J, R^9 and m are as defined as in claim 1, or a pharmaceutically acceptable salt thereof, comprising the steps of reacting the compound of formula I' as defined in claim 1 with an approximately equimolar amount of an oxidizing agent and optionally converting the product into a salt.

9. A process according to claim 8, wherein the oxidizing agent is selected from hydrogen peroxide, peracetic acid, m-chloroperbenzoic acid, sodium hypochlorite or sodium hypobromite.

10. A process according to claim 8 or 9 for producing the following compound

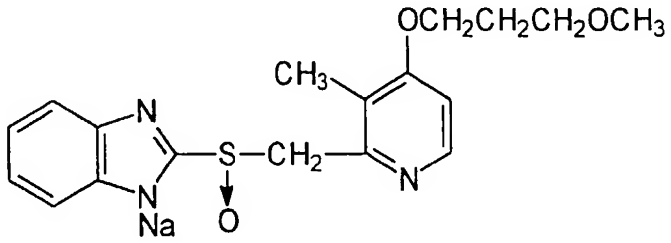


or a pharmaceutically acceptable salt thereof, comprising the steps of reacting the following compound

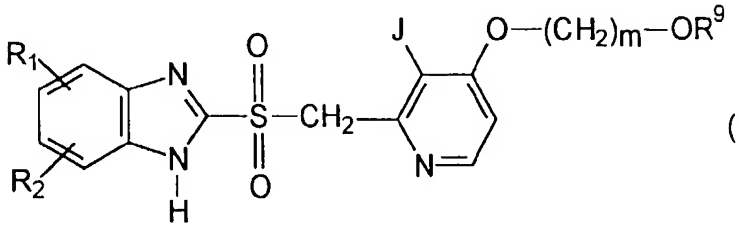


with an approximately equimolar amount of an oxidizing agent and optionally converting the product into a salt.

11. A process as defined in claim 10 for producing a pharmaceutically acceptable salt having the following formula:



12. A process for producing a compound of formula I'''

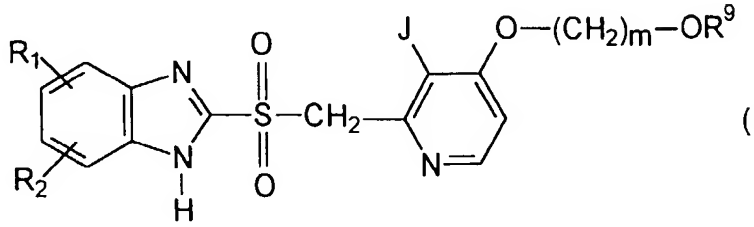


(I''')

wherein R^1, R^2, J, R^9 and m are as defined in claim 1, or a pharmaceutically acceptable salt thereof, comprising the step of reacting the compound of formula I' as defined in claim 1 with at least two molar equivalent amounts of an oxidizing agent, and optionally converting the product into a salt.

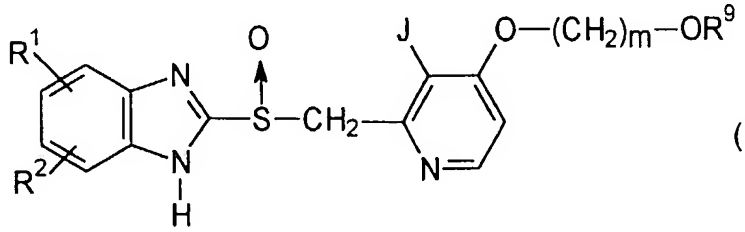
13. A process according to claim 12, wherein the oxidizing agent is selected from hydrogen peroxide, peracetic acid, m-chloroperbenzoic acid, sodium hypochlorite or sodium m-periodate.

14. A process for producing a compound of formula I'''



(I''')

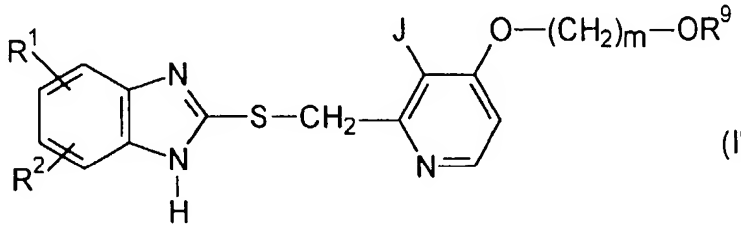
wherein R^1, R^2, J, R^9 and m are as defined in claim 1, or a pharmaceutically acceptable salt thereof, comprising the step of reacting an oxidizing agent with a compound of formula I''



(I'')

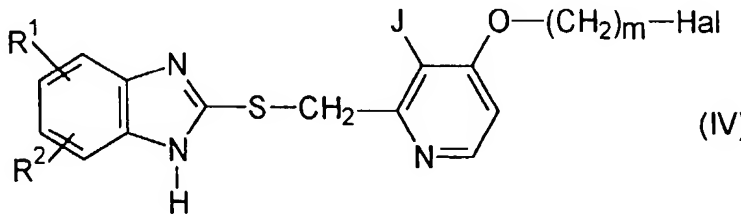
wherein R^1, R^2, J, R^9 and m are as defined above, and optionally converting the product into a salt.

15. A process for producing a compound of the general formula I'



(I')

wherein R^1, R^2, J, m and R^9 are defined as in claim 1 or a pharmaceutically acceptable salt thereof comprising the steps of reacting a compound of the formula IV



(IV)

wherein R^1, R^2, J and m are defined as above and Hal represents a halogen atom, with a compound of formula R^9OH, wherein R^9 is defined as above, and optionally converting the product into a salt.

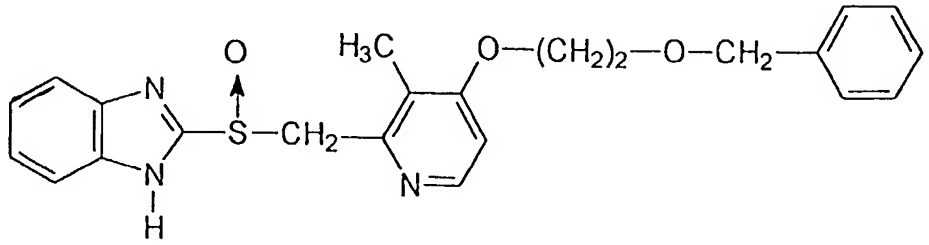
16. A process according to claim 15, wherein the reaction is carried out in the presence of an acid scavenger.

17. A method for preparing a pharmaceutical composition comprising combining a pharmacologically effective amount of a pyridine derivative preparable according to any of the processes as defined in claims 1-6, 8, 10, 11, 15 and 20 or a pharmacologically acceptable salt thereof and a pharmacologically acceptable carrier.

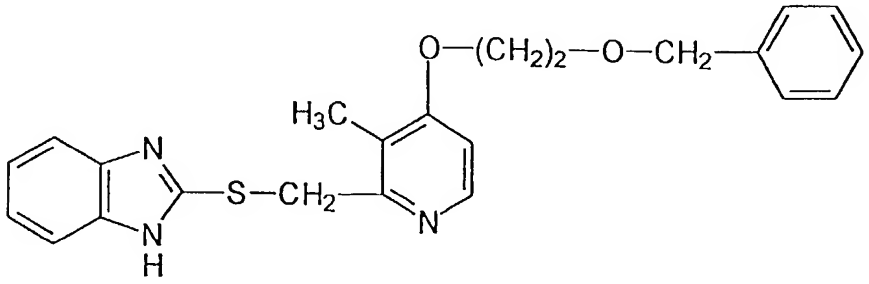
18. A method for preparing a pharmaceutical composition according to claim 17 comprising the use of 0.1 to 100 g of the pyridine derivative or a pharmacologically acceptable salt thereof per unit dose.

19. Use of a pyridine derivative preparable according to any of the processes as defined in claims 1-6, 8, 10, 11, 15 and 20 for the manufacture of a medicament for the treatment or prevention of peptic ulcers.

20. A process for preparing a pyridine derivative of the structural formula



or a pharmaceutically acceptable salt thereof, comprising reacting a compound of the formula



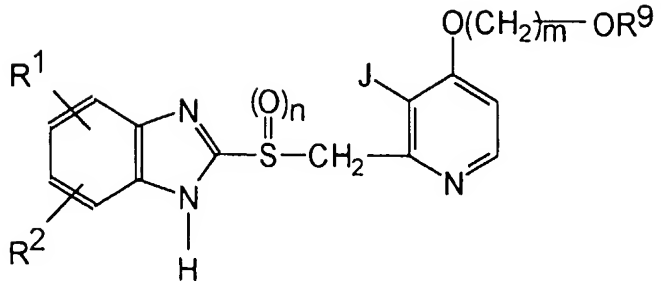
with an approximately equimolar amount of an oxidizing agent and optionally converting the product into a salt.

21. The use of a pyridine derivative according to any of claims 1 to 13 for the manufacture of a medicament for the inhibition of gastric acid secretion.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Pyridinderivat, welches durch die allgemeine Formel:



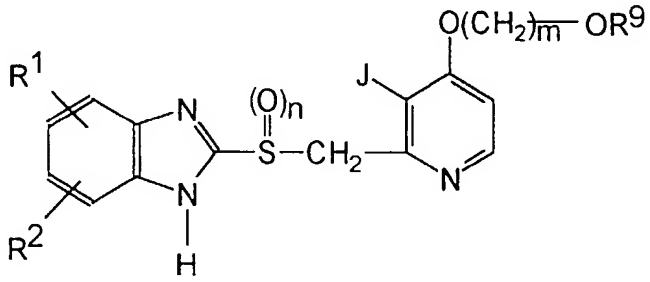
dargestellt ist, wobei R^1 und R^2 gleich oder unterschiedlich sein können und jeweils ein Wasserstoffatom, eine C_1-C_6-Alkyl-, C_1-C_6-Alkoxy-, halogenierte C_1-C_6-Alkyl-, C_1-C_6-Alkoxycarbonyl- oder Carboxylgruppe oder ein Halogenatom bedeuten; J ein C_1-C_6-Alkyl ist; R^9 ein Wasserstoffatom oder eine C_1-C_6-Alkylgruppe ist; n eine ganze Zahl von 0 bis 2 ist, m eine ganze Zahl von 2 bis 10 ist, unter der Voraussetzung, dass, wenn R^9 eine C_1-C_6-Alkylgruppe ist, m eine ganze Zahl von 3 bis 10 bedeutet, und ein pharmazeutisch geeignetes Salz davon.

2. Pyridinderivat nach Anspruch 1, wobei R^1 Wasserstoff oder C_1-C_6-Alkyl ist, und R^2 Wasserstoff ist.

3. Pyridinderivat nach Anspruch 1 oder 2, wobei n 1 ist, R^1 und R^2 beide Wasserstoff bedeuten, oder R^1 5-(C_1-C_6)-Alkyl, 5-halogeniertes (C_1-C_6)-Alkyl oder 5-(C_1-C_6)-Alkoxy ist und R^2 Wasserstoff ist, J Methyl ist und m 3 bis 10 ist, und R^9 C_1-C_6-Alkyl ist.

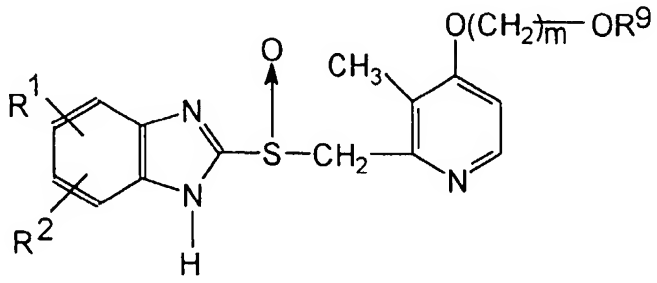
4. Pyridinderivat nach Anspruch 3, wobei R^1 und R^2 beide Wasserstoff bedeuten, J Methyl ist, m 3 ist und R^9 Methyl ist.

5. Pyridinderivat nach Anspruch 1, welches durch die Formel



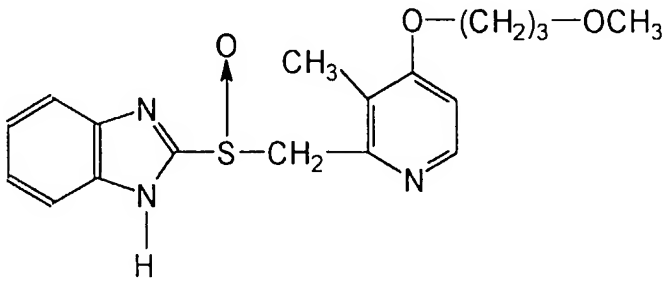
dargestellt ist, in der R^1 und R^2 , welche gleich oder unterschiedlich voneinander sein können, Wasserstoff, C_1-C_6-Alkyl, C_1-C_6-Alkoxy, halogeniertes C_1-C_6-Alkyl, C_1-C_6-Alkoxycarbonyl oder Carboxylgruppe oder ein Halogenatom bedeuten; n eine ganze Zahl von 0 bis 2 ist; J eine C_1-C_6-Alkylgruppe ist; m eine ganze Zahl von 3 bis 10 ist; und R^9 eine C_1-C_6-Alkylgruppe ist; oder ein pharmazeutisch geeignetes Salz davon.

6. Pyridinderivat nach Anspruch 1



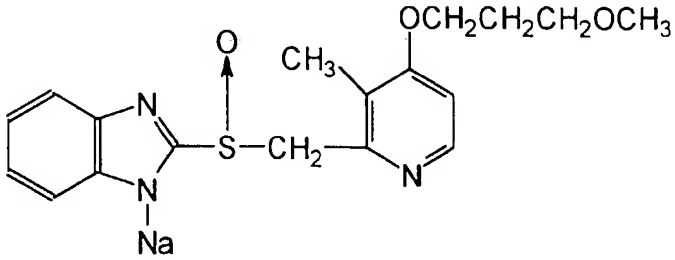
wobei R^1 und R^2, welche gleich oder unterschiedlich voneinander sein können, Wasserstoff, C_1-C_6-Alkyl, C_1-C_6-Alkoxy, halogeniertes C_1-C_6-Alkyl, C_1-C_6-Alkoxycarbonyl oder Carboxylgruppe oder ein Halogenatom bedeuten; m die ganze Zahl 3 ist; und R^9 C_1-C_6-Alkyl ist; oder ein pharmazeutisch geeignetes Salz davon.

7. Pyridinderivat nach Anspruch 1, welches durch die Formel



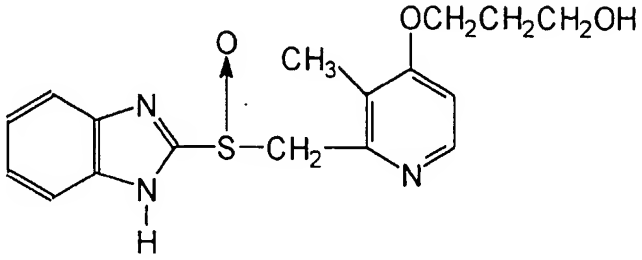
dargestellt ist.

8. Pharmazeutisch geeignetes Salz des Pyridinderivats nach Anspruch 1, welches durch die Formel



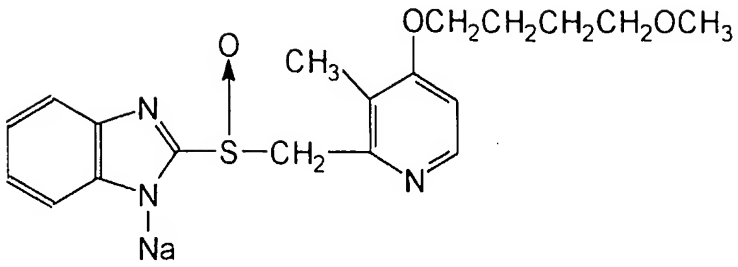
dargestellt ist.

9. Pyridinderivat nach Anspruch 1, welches durch die Formel



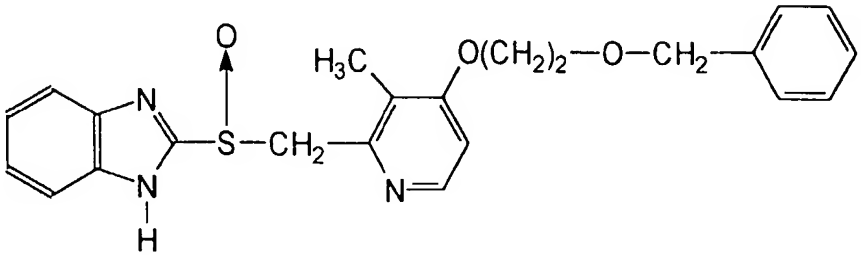
dargestellt ist.

10. Pharmazeutisch geeignetes Salz des Pyridinderivats nach Anspruch 1, welches durch die Formel



dargestellt ist.

11. Pyridinderivat der Strukturformel



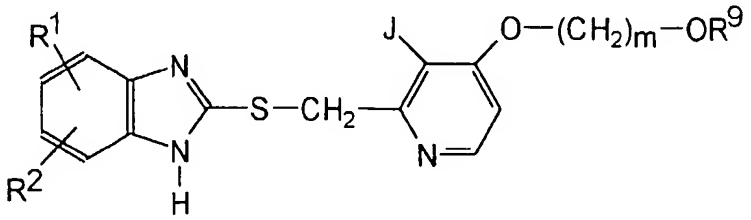
oder ein pharmazeutisch geeignetes Salz davon.

12. Pharmazeutische Zusammensetzung, umfassend eine pharmakologisch wirksame Menge eines Pyridinderivats nach einem der Ansprüche 1 bis 11, worin n 1 ist, oder ein pharmakologisch geeignetes Salz davon und einen pharmakologisch geeigneten Träger.

13. Pharmazeutische Zusammensetzung nach Anspruch 12, umfassend 0,1 bis 100 g des Pyridinderivats oder eines pharmakologisch geeigneten Salzes davon pro Einheitsdosis.

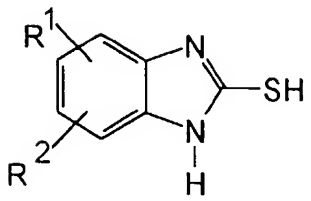
14. Verwendung eines Pyridinderivats nach einem der Ansprüche 1 bis 11, worin n 1 ist, für die Herstellung eines Arzneimittels für die Behandlung oder Prophylaxe von gastrointestinalen Ulci.

15. Verfahren zum Herstellen einer Verbindung der allgemeinen Formel (I')



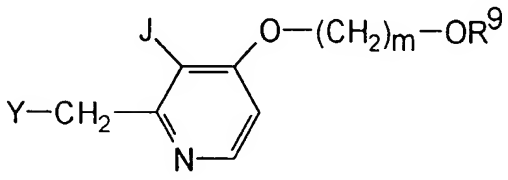
(I')

wobei R^1, R^2, m, R^9 und J wie in Anspruch 1 definiert sind, oder eines pharmazeutisch geeigneten Salzes davon, umfassend die Stufen: Umsetzen der Verbindung der Formel (II)



(II)

wobei R^1 und R^2 wie zuvor angegeben definiert sind, mit der Verbindung der Formel (III)



(III)

wobei J, m und R^9 wie zuvor angegeben definiert sind, und Y ein Halogenatom oder eine Sulfonyloxygruppe darstellt, und gewünschtenfalls Umwandeln des Produkts in ein Salz.

16. Verfahren nach Anspruch 15, wobei Y Chlor, Brom oder Iod darstellt.

17. Verfahren nach Anspruch 15, wobei Y eine Alkylsulfonyloxygruppe darstellt.

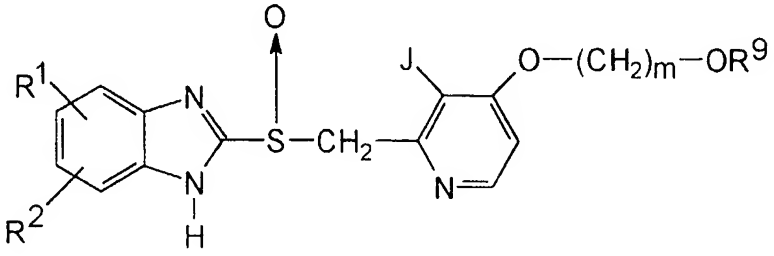
18. Verfahren nach Anspruch 17, wobei die Alkylsulfonyloxygruppe eine Methylsulfonyloxygruppe oder eine Ethylsulfonyloxygruppe ist.

19. Verfahren nach Anspruch 15, wobei die Sulfonyloxygruppe eine aromatische Sulfonyloxygruppe ist.

20. Verfahren nach Anspruch 19, wobei die aromatische Sulfonyloxygruppe eine Benzolsulfonyloxygruppe oder eine Tosyloxygruppe ist.

21. Verfahren nach einem der Ansprüche 15 bis 20, wobei die Reaktion in Anwesenheit eines Säurefängers durchgeführt wird.

22. Verfahren zum Herstellen einer Verbindung der Formel (I")

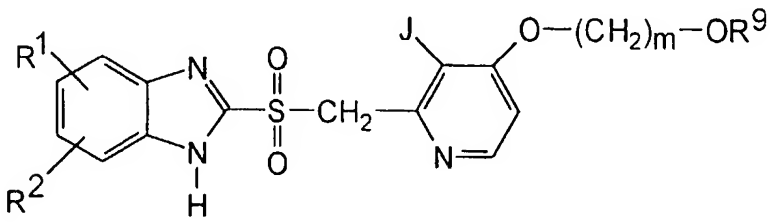


(I")

wobei R^1, R^2, J, m und R^9 wie in Anspruch 1 definiert sind, oder eines pharmazeutisch geeigneten Salzes davon, umfassend die Stufen: Umsetzen der Verbindung der Formel (I') gemäss Anspruch 15, mit einer entsprechenden äquimolaren Menge eines Oxidationsmittels, und gewünschtenfalls Umwandeln des Produkts in ein Salz.

23. Verfahren nach Anspruch 22, wobei das Oxidationsmittel aus Wasserstoffperoxid, Peressigsäure, m-Chlorperbenzoesäure, Natriumhypochlorit oder Natriumhypobromit ausgewählt wird.

24. Verfahren zum Herstellen einer Verbindung der Formel (I''')

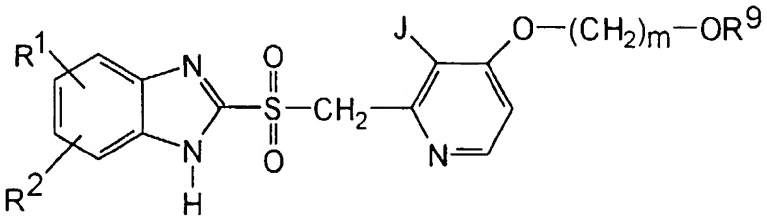


(I''')

wobei R^1, R^2, J, R^9 und m wie in Anspruch 1 angegeben definiert sind, oder eines pharmazeutisch geeigneten Salzes davon, umfassend die Stufe: Umsetzen der Verbindung der Formel (I') gemäss Anspruch 15 mit mindestens zwei molaräquivalenten Mengen eines Oxidationsmittels, und gewünschtenfalls Umwandeln des Produkts in ein Salz.

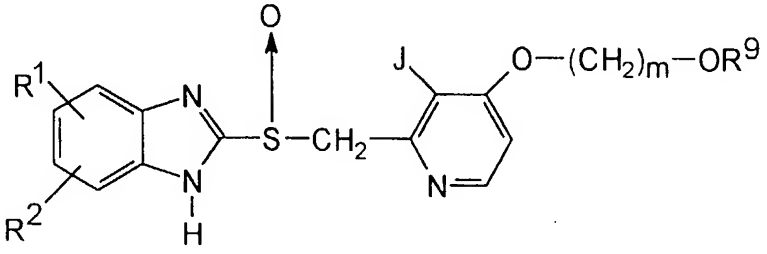
25. Verfahren gemäss Anspruch 24, wobei das Oxidationsmittel aus Wasserstoffperoxid, Peressigsäure, m-Chlorperbenzoesäure, Natriumhypochlorit oder Natrium-m-periodat ausgewählt wird.

26. Verfahren zum Herstellen der Verbindung der Formel (I''')



(I''')

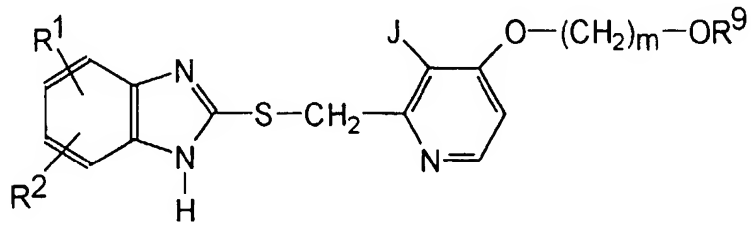
wobei R^1, R^2, J, R^9 und m wie in Anspruch 1 definiert sind, oder eines pharmazeutisch geeigneten Salzes davon, umfassend die Stufe: Umsetzen eines Oxidationsmittels mit der Verbindung der Formel (I")



(I")

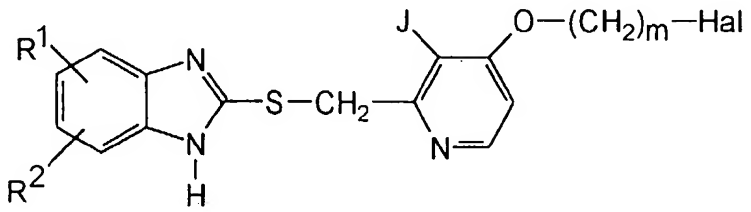
wobei R^1, R^2, J, R^9 und m wie zuvor angegeben definiert sind, und gewünschtenfalls Umwandeln des Produkts in ein Salz.

27. Verfahren zum Herstellen einer Verbindung der allgemeinen Formel (I')



(I')

wobei R^1, R^2, J, m und R^9 wie in Anspruch 1 definiert sind, oder eines pharmazeutisch geeigneten Salzes davon, umfassend die Stufen: Umsetzen einer Verbindung der Formel (IV)



(IV)

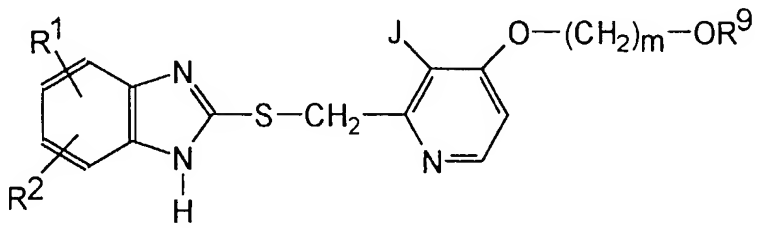
wobei R^1, R^2, J und m wie zuvor angegeben definiert sind, und Hal ein Halogenatom darstellt, mit einer Verbindung der Formel R^9OH, wobei R^9 wie zuvor angegeben definiert ist, und gewünschtenfalls Umwandeln des Produkts in ein Salz.

28. Verfahren gemäss Anspruch 27, wobei die Reaktion in Gegenwart eines Säurefängers durchgeführt wird.

29. Verwendung eines Pyridinderivats gemäss einem der Ansprüche 1 bis 11, worin n 1 ist, für die Herstellung eines Arzneimittels für die Inhibierung der Magensäuresekretion.

Patentansprüche für folgende Vertragsstaten : ES, GR

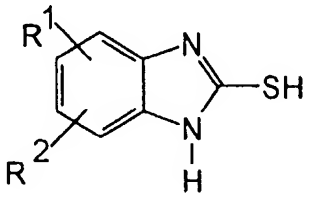
1. Verfahren zum Herstellen einer Verbindung der allgemeinen Formel (I')



(I')

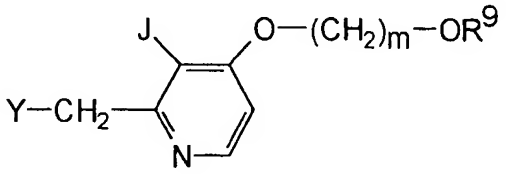
wobei R^1 und R^2 gleich oder unterschiedlich voneinander sein können und jeweils ein Wasserstoffatom, eine C_1-C_6-Alkyl-, C_1-C_6-Alkoxy-, halogenierte C_1-C_6-Alkyl-, C_1-C_6-Alkoxycarbonyl- oder Carboxylgruppe oder ein Halogenatom bedeuten; J ein C_1-C_6-Alkyl ist; R^9 ein Wasserstoffatom oder eine C_1-C_6-Alkylgruppe ist; m eine ganze Zahl von 2 bis 10 ist, unter der Voraussetzung, dass, wenn R^9 eine C_1-C_6-Alkylgruppe ist, m eine ganze Zahl von

3 bis 10 bedeutet; oder eines pharmazeutisch geeigneten Salzes davon, umfassend die Stufen: Umsetzen der Verbindung der Formel (II)



(II)

wobei R^1 und R^2 wie zuvor angegeben definiert sind, mit der Verbindung der Formel (III)



(III)

wobei J, m und R^9 wie zuvor angegeben definiert sind, und Y ein Halogenatom oder eine Sulfonyloxygruppe darstellt, und gewünschtenfalls Umwandeln des Produkts in ein Salz.

2. Verfahren nach Anspruch 1, wobei Y Chlor, Brom oder Iod darstellt.

3. Verfahren nach Anspruch 1, wobei Y eine Alkylsulfonyloxygruppe ist.

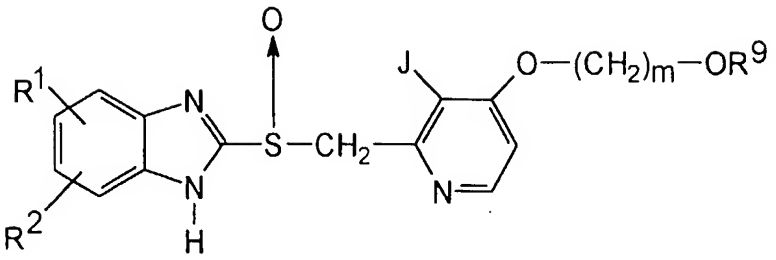
4. Verfahren nach Anspruch 3, wobei die Alkylsulfonyloxygruppe eine Methylsulfonyloxygruppe oder eine Ethylsulfonyloxygruppe ist.

5. Verfahren nach Anspruch 1, wobei die Sulfonyloxygruppe eine aromatische Sulfonyloxygruppe ist.

6. Verfahren nach Anspruch 5, wobei die aromatische Sulfonyloxygruppe eine Benzolsulfonyloxygruppe oder eine Tosyloxygruppe ist.

7. Verfahren nach einem der Ansprüche 1 bis 6, wobei die Reaktion in Anwesenheit eines Säurefängers durchgeführt wird.

8. Verfahren zum Herstellen einer Verbindung der Formel (I")

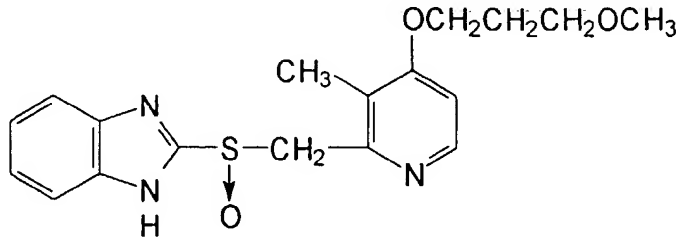


(I")

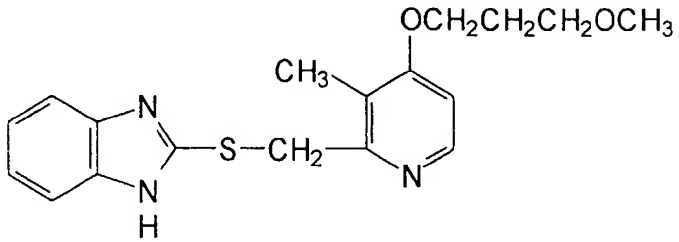
wobei R^1, R^2, J, m und R^9 wie in Anspruch 1 definiert sind, oder eines pharmazeutisch geeigneten Salzes davcn, umfassend die Stufen: Umsetzen der Verbindung der Formel (I'), wie in Anspruch 1 definiert, mit einer annähernd äquimolaren Menge eines Oxidationsmittels und, gewünschtenfalls, Umwandeln des Produkts in ein Salz.

9. Verfahren nach Anspruch 8, wobei das Oxidationsmittel aus Wasserstoffperoxid, Peressigsäure, m-Chlorperbenzoesäure, Natriumhypochlorit oder Natriumhypobromit ausgewählt wird.

10. Verfahren nach Anspruch 8 oder 9 zur Herstellung der folgenden Verbindung

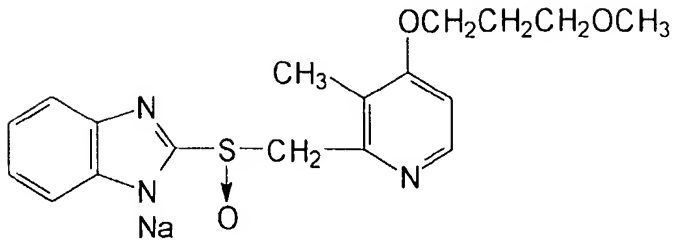


oder eines pharmazeutisch geeigneten Salzes davon, umfassend: Umsetzen der folgenden Verbindung

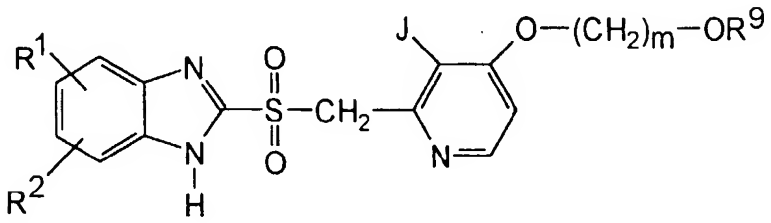


mit einer annähernd äquimolaren Menge eines Oxidationsmittels und, gewünschtenfalls, Umwandeln des Produkts in ein Salz.

11. Verfahren gemäß Anspruch 10 zur Herstellung eines pharmazeutisch akzeptablen Salzes mit der folgenden Formel:



12. Verfahren zum Herstellen einer Verbindung der Formel (I''')

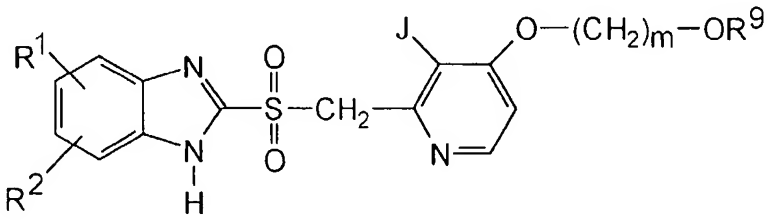


(I''')

wobei R^1, R^2, J, R^9 und m wie in Anspruch 1 definiert sind, oder eines pharmazeutisch geeigneten Salzes davon, umfassend die Stufe: Umsetzen der Verbindung der Formel (I'), wie in Anspruch 1 definiert, mit mindestens zwei molaräquivalenten Mengen eines Oxidationsmittels, und, gewünschtenfalls, Umwandeln des Produkts in ein Salz.

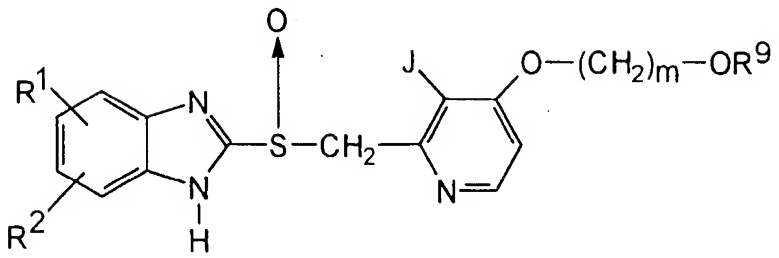
13. Verfahren gemäss Anspruch 10, wobei das Oxidationsmittel aus Wasserstoffperoxid, Peressigsäure, m-Chlorperbenzoesäure, Natriumhypochlorit oder Natrium-m-periodat ausgewählt wird.

14. Verfahren zum Herstellen der Verbindung der Formel (I''')



(I''')

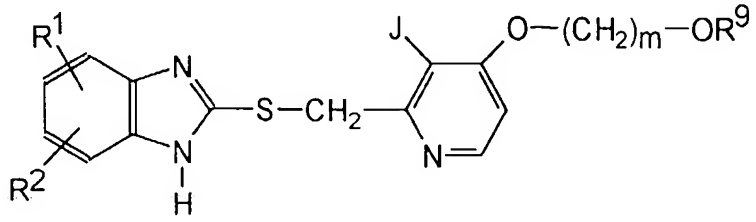
wobei R^1, R^2, J, R^9 und m wie in Anspruch 1 definiert sind, oder eines pharmazeutisch geeigneten Salzes davon, umfassend die Stufe: Umsetzen eines Oxidationsmittels mit der Verbindung der Formel (I'')



(I")

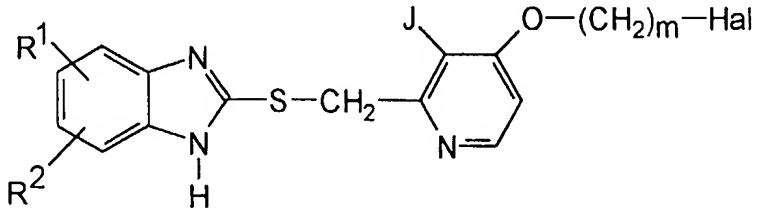
wobei R^1, R^2, J, R^9 und m wie zuvor angegeben definiert sind, und, gewünschtenfalls, Umwandeln des Produkts in ein Salz.

15. Verfahren zum Herstellen einer Verbindung der allgemeinen Formel (I')



(I')

wobei R^1, R^2, J, m und R^9 wie in Anspruch 1 definiert sind, oder eines pharmazeutisch geeigneten Salzes davon, umfassend die Stufen: Umsetzen einer Verbindung der Formel (IV)



(IV)

wobei R^1, R^2, J und m wie zuvor angegeben definiert sind und Hal ein Halogenatom darstellt, mit einer Verbindung der Formel R^9OH, wobei R^9 wie zuvor angegeben definiert ist, und, gewünschtenfalls, Umwandeln des Produkts in ein Salz.

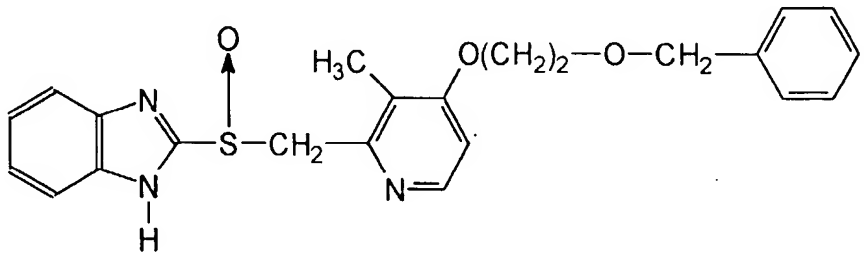
16. Verfahren gemäss Anspruch 13, wobei die Reaktion in Anwesenheit eines Säurefängers durchgeführt wird.

17. Verfahren zum Herstellen einer pharmazeutischen Zusammensetzung, umfassend: Verbinden einer pharmakologisch wirksamen Menge eines Pyridinderivats, welches gemäss einem der Verfahren, wie in den Ansprüchen 1 bis 6, 8, 10, 12, 13 und 18 definiert, herstellbar ist, oder eines pharmakologisch geeigneten Salzes davon mit einem pharmakologisch geeigneten Träger.

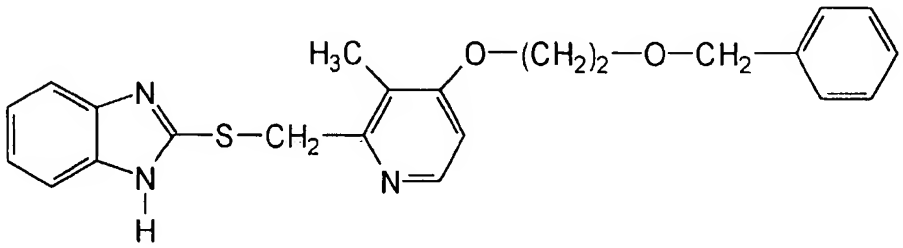
18. Verfahren zum Herstellen einer pharmazeutischen Zusammensetzung gemäss Anspruch 15, umfassend die Verwendung von 0,1 bis 100 g des Pyridinderivats oder eines pharmakologisch geeigneten Salzes davon pro Einheitsdosis.

19. Verwendung eines Pyridinderivats, welches gemäss einem der in den Ansprüchen 1 bis 6, 8, 10, 12, 13 und 18 definierten Verfahren herstellbar ist, für die Herstellung eines Arzneimittels für die Behandlung oder Prophylaxe von gastrointestinalen Ulci.

20. Verfahren zum Herstellen eines Pyridinderivats der Strukturformel



oder eines pharmazeutisch geeigneten Salzes davon, umfassend: Umsetzen einer Verbindung der Formel



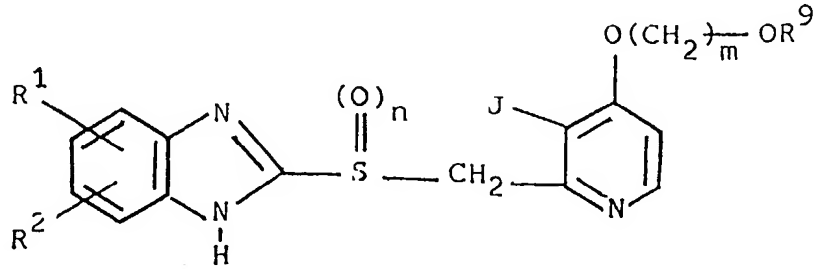
mit einer annähernd äquimolaren Menge eines Oxidationsmittels und, gewünschtenfalls, Umwandeln des Produkts in ein Salz.

21. Verwendung eines Pyridinderivats gemäss einem der Ansprüche 1 bis 11 für die Herstellung eines Arzneimittels für die Inhibierung der Magensäuresekretion.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Dérivé de pyridine représenté par la formule générale :



dans laquelle

R^1 et R^2 peuvent être identiques ou différents et représentent chacun un atome d'hydrogène, un groupe alkyle en C_1-C_6, alcoxy en C_1-C_6, alkyle en C_1-C_6 halogéné, alcoxycarbonyle en C_1-C_6 ou carboxyle ou un atome d'halogène ;

J est un groupe alkyle en C_1-C_6,

R^9 représente un atome d'hydrogène ou un groupe alkyle en C_1-C_6,

n représente un nombre entier de 0 à 2,

m représente un nombre entier de 2 à 10,

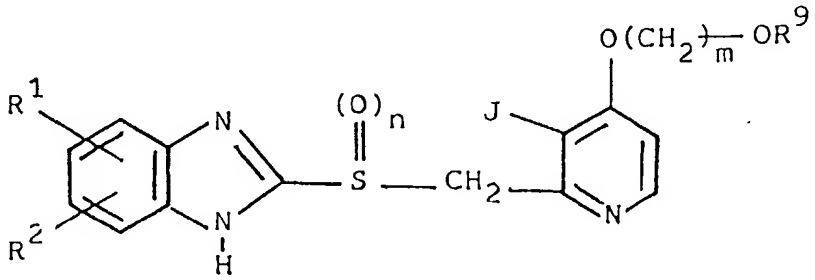
avec la condition que si R^9 est un groupe alkyle en C_1-C_6, m représente un nombre entier de 3 à 10, et un sel pharmaceutiquement acceptable de ce dérivé.

2. Dérivé de pyridine selon la revendication 1, dans lequel R^1 est l'hydrogène ou un groupe alkyle en C_1-C_6 et R^2 est l'hydrogène.

3. Dérivé de pyridine selon la revendication 1 ou 2, dans lequel n est 1, R^1 et R^2 sont tous deux de l'hydrogène ou bien R^1 est un groupe alkyle en C_1-C_6 à la position 5, alkyle en C_1-C_6 halogéné à la position 5 ou alcoxy en C_1-C_6 à la position 5 et R^2 est l'hydrogène, J est le groupe méthyle et m est de 3 à 10, et R^9 est un groupe alkyle en C_1-C_6.

4. Dérivé de pyridine selon la revendication 3, dans lequel R^1 et R^2 sont tous deux de l'hydrogène, J est le groupe méthyle, m est 3 et R^9 est le groupe méthyle.

5. Dérivé de pyridine selon la revendication 1, représenté par la formule



dans laquelle

R^1 et R^2, qui peuvent être identiques ou différents, représentent chacun l'hydrogène, un groupe alkyle en C_1-C_6, alcoxy en C_1-C_6, alkyle en C_1-C_6 halogéné, alcoxycarbonyle en C_1-C_6 ou carboxyle, ou un atome d'halogène ;

n est un nombre entier de 0 à 2,

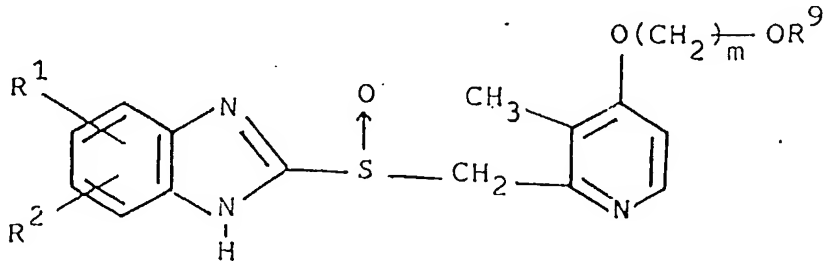
J est un groupe alkyle en C_1-C_6,

m est un nombre entier de 3 à 10, et

R^9 est un groupe alkyle en C_1-C_6 ;

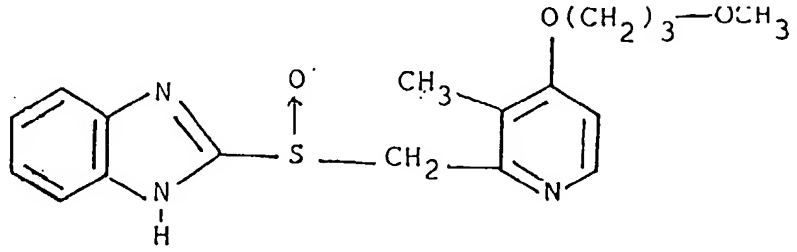
ou un sel pharmaceutiquement acceptable de ce dérivé.

6. Dérivé de pyridine selon la revendication 1

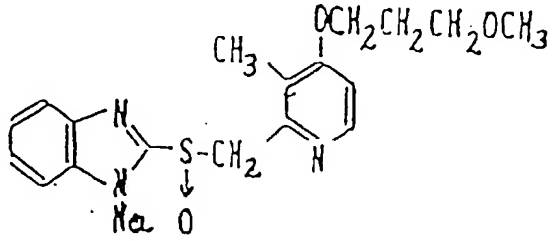


dans lequel R^1 et R^2, qui peuvent être identiques ou différents, représentent chacun l'hydrogène, un groupe alkyle en C_1-C_6, alcoxy en C_1-C_6, alkyle en C_1-C_6 halogéné, alcoxycarbonyle en C_1-C_6 ou carboxyle, ou un atome d'halogène ; m est le nombre entier 3, et R^9 est un groupe alkyle en C_1-C_6, ou un sel pharmaceutiquement acceptable de ce dérivé.

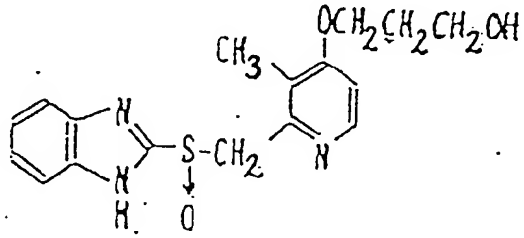
7. Dérivé de pyridine selon la revendication 1, représenté par la formule



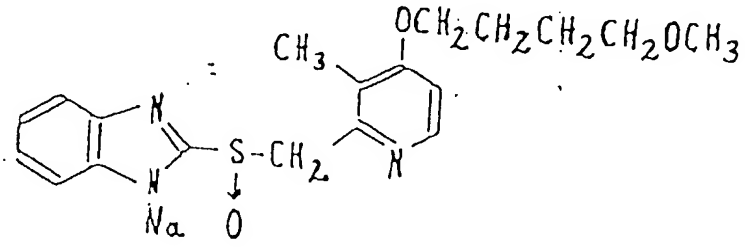
8. Sel pharmaceutiquement acceptable du dérivé de pyridine selon la revendication 1, représenté par la formule



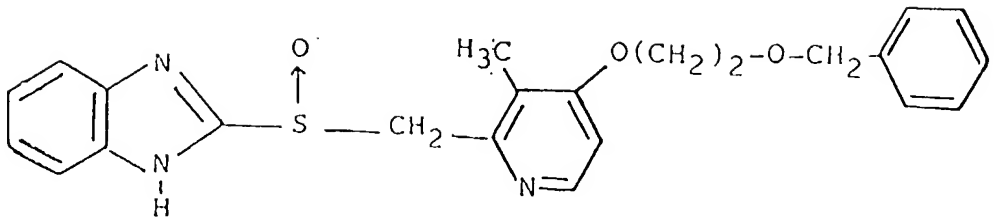
9. Dérivé de pyridine selon la revendication 1, représenté par la formule



10. Sel pharmaceutiquement acceptable du dérivé de pyridine selon la revendication 1, représenté par la formule



11. Dérivé de pyridine ayant la formule développée



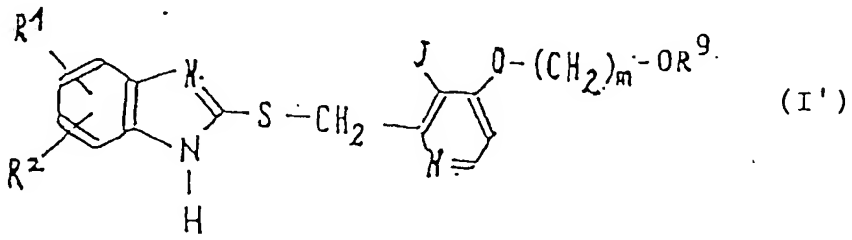
ou un sel pharmaceutiquement acceptable de ce dérivé.

12. Composition pharmaceutique qui comprend une quantité pharmacologiquement efficace d'un dérivé de pyridine selon l'une quelconque des revendications 1 à 11 où n est 1 ou d'un sel pharmaceutiquement acceptable de celui-ci et un support pharmacologiquement acceptable.

13. Composition pharmaceutique selon la revendication 12, qui comprend 0,1 à 100 grammes du dérivé de pyridine ou d'un sel pharmacologiquement acceptable de celui-ci par dose unitaire.

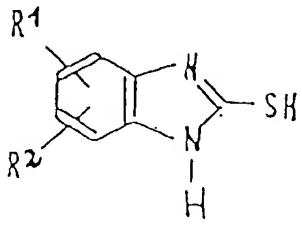
14. Utilisation d'un dérivé de pyridine selon l'une quelconque des revendications 1 à 11 où n est 1 pour la fabrication d'un médicament destiné au traitement ou à la prévention d'ulcères gastroduodénaux.

15. Procédé de production d'un composé de formule générale I'



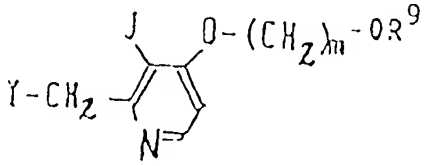
(I')

où R^1, R^2, m, R^9 et J sont tels que définis dans la revendication 1,
ou d'un sel pharmaceutiquement acceptable de celui-ci, comprenant les étapes de réaction du composé de formule II



(II)

où R^1 et R^2 sont tels que définis ci-dessus, avec le composé de formule III



(III)

où J, m et R^9 sont tels que définis ci-dessus et
Y représente un atome d'halogène ou un groupe sulfonyloxy, et facultativement de conversion du produit en un sel.

16. Procédé selon la revendication 15, dans lequel Y représente le chlore, le brome ou l'iode.

17. Procédé selon la revendication 15, dans lequel Y représente un groupe alkylsulfonyloxy.

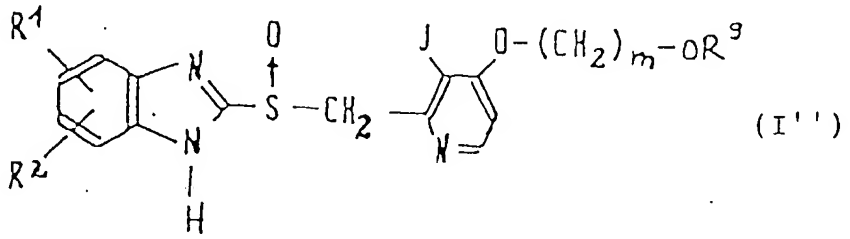
18. Procédé selon la revendication 17, dans lequel le groupe alkylsulfonyloxy est un groupe méthylsulfonyloxy ou un groupe éthylsulfonyloxy.

19. Procédé selon la revendication 15, dans lequel le groupe sulfonyloxy est un groupe sulfonyloxy aromatique.

20. Procédé selon la revendication 19, dans lequel le groupe sulfonyloxy aromatique est un groupe benzène-sulfonyloxy ou un groupe tosyloxy.

21. Procédé selon l'une quelconque des revendications 15 à 20, dans lequel la réaction est conduite en présence d'un accepteur d'acide.

22. Procédé de production d'un composé de formule I''

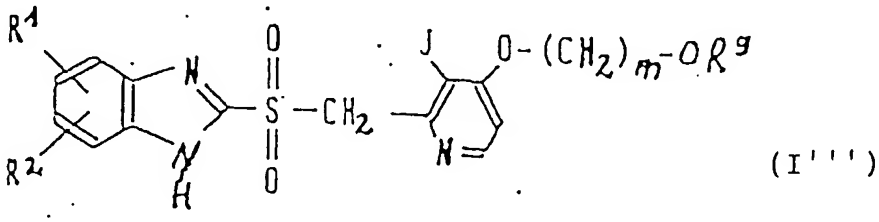


(I'')

où R^1, R^2, J, m et R^9 sont tels que définis dans la revendication 1,
ou d'un sel pharmaceutiquement acceptable de celui-ci, comprenant les étapes de réaction du composé de formule I' tel que défini dans la revendication 15 avec une quantité approximativement équimolaire d'un agent oxydant et, facultativement, de conversion du produit en un sel.

23. Procédé selon la revendication 22, dans lequel l'agent oxydant est choisi parmi le peroxyde d'hydrogène, l'acide peracétique, l'acide *m*-chloroperbenzoïque, l'hypochlorite de sodium et l'hypobromite de sodium.

24. Procédé de production d'un composé de formule I'''

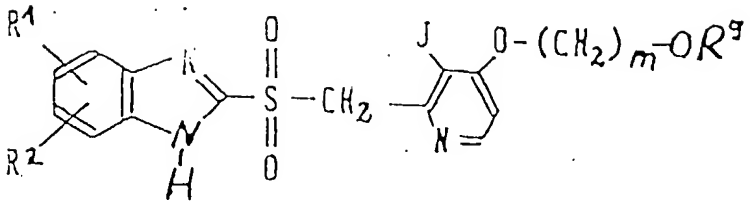


(I''')

où R^1, R^2, J, R^9 et m sont tels que définis dans la revendication 1,
ou d'un sel pharmaceutiquement acceptable de celui-ci, comprenant les étapes de réaction du composé de formule I' tel que défini dans la revendication 15 avec au moins deux équivalents molaires d'un agent oxydant, et facultativement de conversion du produit en un sel.

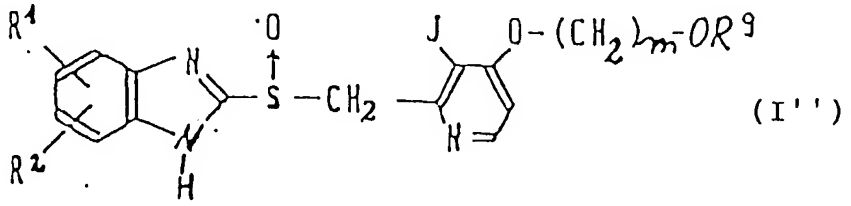
25. Procédé selon la revendication 24, dans lequel l'agent oxydant est choisi parmi le peroxyde d'hydrogène, l'acide peracétique, l'acide *m*-chloroperbenzoïque, l'hypochlorite de sodium et le *m*-periodate de sodium.

26. Procédé de production du composé de formule I'''



(I''')

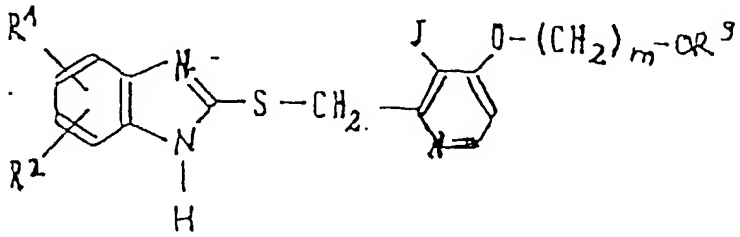
où R^1, R^2, J, R^9 et m sont tels que définis dans la revendication 1,
ou d'un sel pharmaceutiquement acceptable de celui-ci, comprenant les étapes de réaction d'un agent oxydant avec le composé de formule I"



(I'')

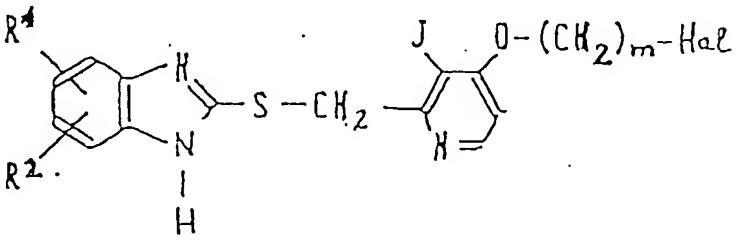
où R^1, R^2, J, R^9 et m sont tels que définis ci-dessus,
et, facultativement, de conversion du produit en un sel.

27. Procédé de production d'un composé de formule générale I'



(I')

où R^1, R^2, J, m et R^9 sont tels que définis dans la revendication 1,
ou d'un sel pharmaceutiquement acceptable de celui-ci, comprenant les étapes de réaction d'un composé de formule IV



(IV)

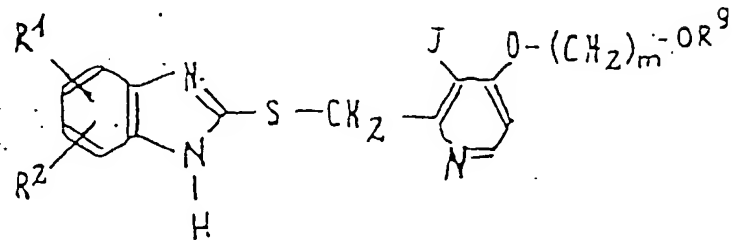
où R^1, R^2, J et m sont tels que définis ci-dessus et Hal représente un atome d'halogène,
avec un composé de formule R^9OH, où R^9 est tel que défini ci-dessus, et, facultativement, de conversion du produit en un sel.

28. Procédé selon la revendication 27, dans lequel la réaction est conduite en présence d'un accepteur d'acide.

29. Utilisation d'un dérivé de pyridine selon l'une quelconque des revendications 1 à 11 où n est 1 pour la fabrication d'un médicament destiné à l'inhibition de la sécrétion d'acide gastrique.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de production d'un composé de la formule générale I'



(I')

dans laquelle

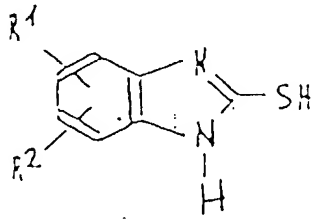
R^1 et R^2 peuvent être identiques ou différents et représentent chacun un atome d'hydrogène, un groupe alkyle en C_1-C_6, alcoxy en C_1-C_6, alkyle en C_1-C_6 halogéné, alcoxycarbonyle en C_1-C_6 ou carboxyle, ou un atome d'halogène ;

J est un groupe alkyle en C_1-C_6,

R^9 représente un atome d'hydrogène ou un groupe alkyle en C_1-C_6,

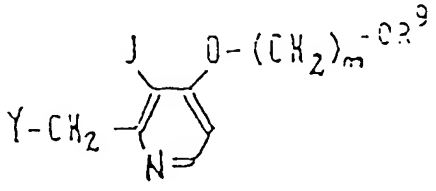
m représente un nombre entier de 2 à 10,

avec la condition que si R^9 est un groupe alkyle en C_1-C_6, m représente un nombre entier de 3 à 10, ou d'un sel pharmaceutiquement acceptable de ce composé, qui comprend les étapes de réaction du composé de formule II



(II)

où R^1 et R^2 sont tels que définis ci-dessus, avec le composé de formule III



(III)

où J, m et R^9 sont tels que définis ci-dessus et Y représente un atome d'halogène ou un groupe sulfonyloxy, et, facultativement, de conversion du produit en un sel.

2. Procédé selon la revendication 1, dans lequel Y représente le chlore, le brome ou l'iode.

3. Procédé selon la revendication 1, dans lequel Y représente un groupe alkylsulfonyloxy.

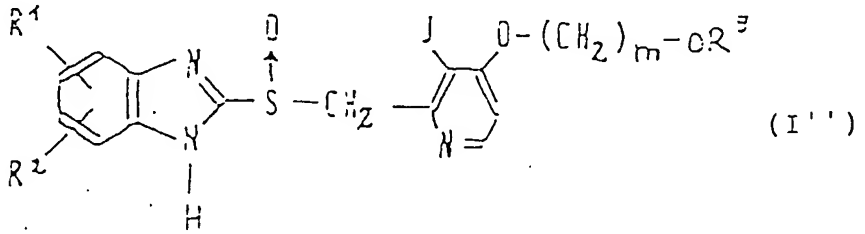
4. Procédé selon la revendication 3, dans lequel le groupe alkylsulfonyloxy est un groupe méthylsulfonyloxy ou un groupe éthylsulfonyloxy.

5. Procédé selon la revendication 1, dans lequel le groupe sulfonyloxy est un groupe sulfonyloxy aromatique.

6. Procédé selon la revendication 5, dans lequel le groupe sulfonyloxy aromatique est un groupe benzène-sulfonyloxy ou un groupe tosyloxy.

7. Procédé selon l'une quelconque des revendications 1 à 6, dans lequel la réaction est conduite en présence d'un accepteur d'acide.

8. Procédé de production d'un composé ce formule I''

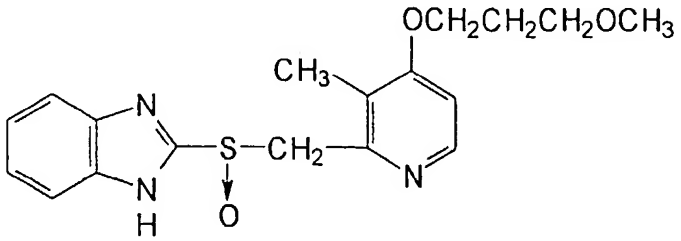


(I'')

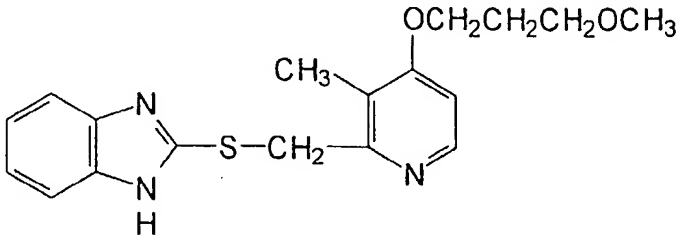
où R^1, R^2, J, m et R^9 sont tels que définis dans la revendication 1,
ou d'un sel pharmaceutiquement acceptable de celui-ci, comprenant les étapes de réaction du composé de formule I' tel que défini dans la revendication 1 avec une quantité approximativement équimolaire d'un agent oxydant et, facultativement, de conversion du produit en un sel.

9. Procédé selon la revendication 8, dans lequel l'agent oxydant est choisi parmi le peroxyde d'hydrogène, l'acide peracétique, l'acide *m*-chloroperbenzoïque, l'hypochlorite de sodium et l'hypobromite de sodium.

10. Procédé selon la revendication 8 ou 9 de production du composé suivante



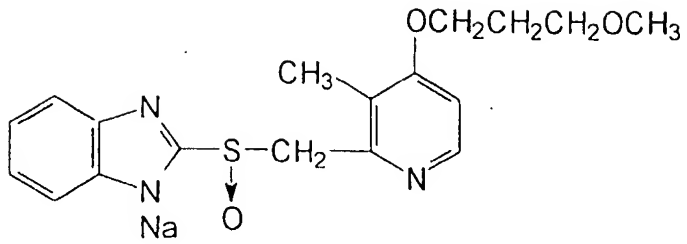
ou d'un sel pharmaceutiquement acceptable de celui-ci, comprenant les étapes de réaction du composé suivante



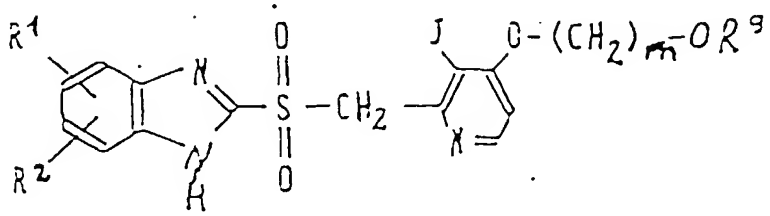
avec une quantité approximativement équimolaire d'un oxydant et, facultativement, de conversion du produit en un sel.

11. Procédé tels que définis dans la revendication 10, de production d'un sel pharmaceutiquement acceptable de

formule suivante:



12. Procédé de production d'un composé de formule I'''

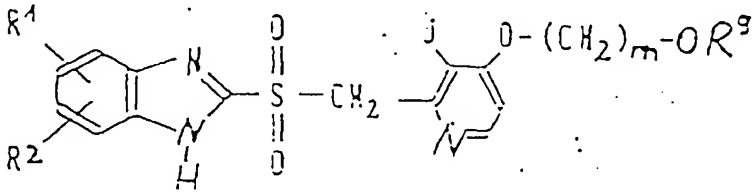


(I''')

où R^1, R^2, J, R^9 et m sont tels que définis dans la revendication 1,
ou d'un sel pharmaceutiquement acceptable de celui-ci, comprenant les étapes de réaction du composé de formule I' tel que défini dans la revendication 1 avec au moins deux équivalents molaires d'un agent oxydant, et, facultativement, de conversion du produit en un sel.

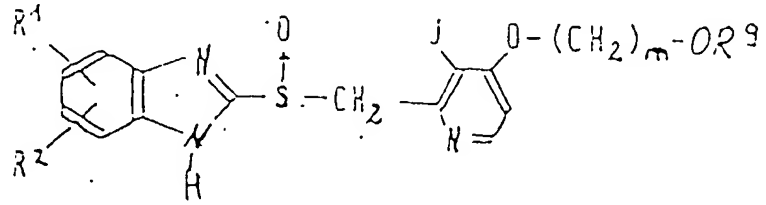
13. Procédé selon la revendication 12, dans lequel l'agent oxydant est choisi parmi le peroxyde d'hydrogène, l'acide peracétique, l'acide *m*-chloroperbenzoïque, l'hypochlorite de sodium et le *m*-periodate de sodium.

14. Procédé de production du composé de formule I'''



(I''')

où R^1, R^2, J, R^9 et m sont tels que définis dans la revendication 1,
ou d'un sel pharmaceutiquement acceptable de celui-ci, comprenant les étapes de réaction d'un agent oxydant avec le composé de formule I''

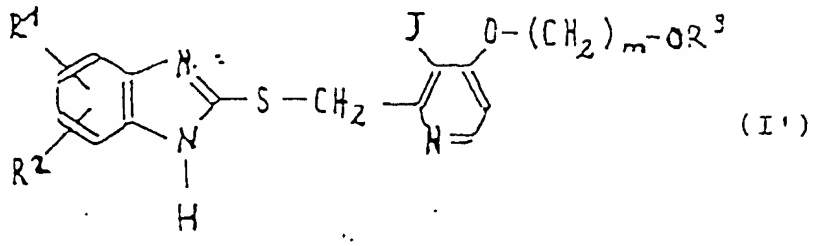


(I'')

où R^1, R^2, J, R^9 et m sont tels que définis ci-dessus,

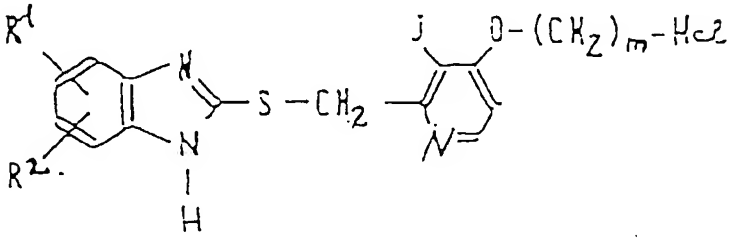
et, facultativement, de conversion du produit en un sel.

15. Procédé de production d'un composé de formule générale I'



(I')

où R^1, R^2, J, m et R^9 sont tels que définis dans la revendication 1,
ou d'un sel pharmaceutiquement acceptable de celui-ci, comprenant les étapes de réaction d'un composé de formule IV



(IV)

où R^1, R^2, J et m sont tels que définis ci-dessus et Hal représente un atome d'halogène,
avec un composé de formule R^9OH, où R^9 est tel que défini ci-dessus, et, facultativement, de conversion du produit en un sel.

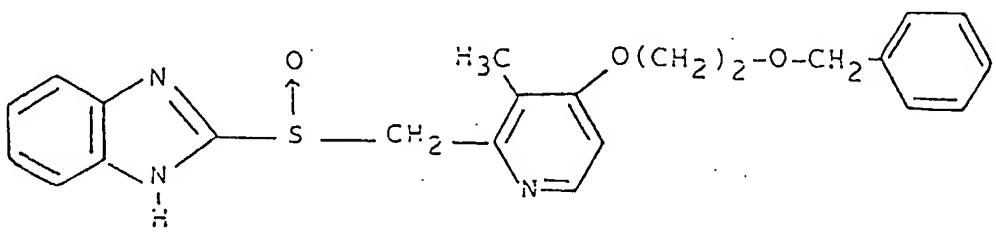
16. Procédé selon la revendication 15, dans lequel la réaction est conduite en présence d'un accepteur d'acide.

17. Procédé de préparation d'une composition pharmaceutique comprenant la mise en association d'une quantité pharmacologiquement efficace d'un dérivé de pyridine pouvant être préparé selon l'un quelconque des procédés tels que définis dans les revendications 1 à 6, 8, 10, 11, 15 et 20, ou d'un sel pharmacologiquement acceptable de ce dérivé, et d'un support pharmacologiquement acceptable.

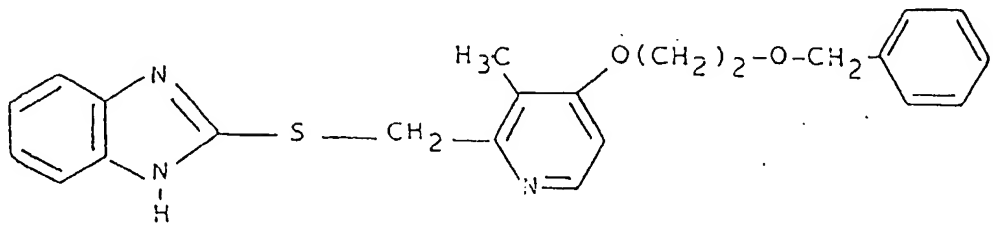
18. Procédé de préparation d'une composition pharmaceutique selon la revendication 17, comprenant l'utilisation de 0,1 à 100 g du dérivé de pyridine ou d'un sel pharmacologiquement acceptable de celui-ci par dose unitaire.

19. Utilisation d'un dérivé de pyridine pouvant être préparé selon l'un quelconque des procédés tels que définis dans les revendications 1 à 6, 8, 10, 11, 15 et 20 pour la fabrication d'un médicament destiné au traitement ou à la prévention d'ulcères gastroduodénaux.

20. Procédé de préparation d'un dérivé de pyridine de formule développée



ou d'un sel pharmaceutiquement acceptable de celui-ci, comprenant la réaction d'un composé de formule



avec une quantité approximativement équimolaire d'un agent oxydant et, facultativement, la conversion du produit en un sel.

21. Utilisation d'un dérivé de pyridine selon l'une quelconque des revendications 1 à 13 pour la fabrication d'un médicament destiné à l'inhibition de la sécrétion d'acide gastrique.